ANNALS OF
INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 33(O.S., Vol. XXXVII)   OCTOBER, 1950   NUMBER 4

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1. Gastroenterology *13*:275 (Oct.) 1949. 2. N. Y. State J. Med. *48*:1822 (Aug.) 1948.

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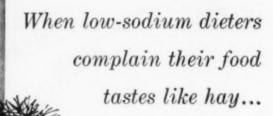
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CORTISONE *

By EDWARD C. KENDALL, Ph.D.,
Rochester, Minnesota

THE name John Phillips has been remembered by the American College of Physicians on fourteen previous occasions. This afternoon I have been asked to give the fifteenth John Phillips Lecture, and at this time I wish to express my appreciation for the honor which has thus been conferred on me. Dr. Phillips spent his active life in the field of clinical medicine. It is my special pleasure to honor his memory by a report of the progress in clinical medicine which has been made possible by contributions from the field of biochemistry.

During the past 20 years an unusual and interesting situation has developed which concerns two spheres of research. These have appeared to be widely separated, but in reality they are two parts of but one problem. I refer to investigations concerned on the one hand with the so-called collagen diseases, and on the other hand with the chemical nature of the adrenal cortex.

The adrenal cortex is the last of the ductless glands to yield its secrets to the investigator. It was shown to be essential to life before anything was known about the chemical nature of its hormones, but even after these had been separated in crystalline form and their chemical structure had been established,[1] the rôle of the adrenal cortex in health and in disease remained obscure. Some progress was made when it was shown that some of the hormones of the adrenal cortex markedly influenced the metabolism of sodium, potassium and chloride, but it became evident that control of these electrolytes was but a partial answer.[2] Patients who had Addison's disease were not restored to a normal condition either by regulation of the intake of salts in the food or by the administration of desoxycorticosterone.

Investigation of the influence of the crystalline hormones of the adrenal cortex, with an atom of oxygen at C-11, on animals indicated that these compounds possess unique properties, but they were so limited in amount that they could not be used in the human being. There was speculation that these

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* Presented as the John Phillips Memorial Lecture at the Thirty-first Annual Session of the American College of Physicians, Boston, Massachusetts, April 19, 1950.

hormones would be of value for substitution therapy in Addison's disease, and there was hope that they would be useful in the treatment of shock, traumatic injuries, burns, and some types of infection, but beyond this there was no place for any product of the adrenal cortex in clinical medicine.

This situation culminated suddenly in 1948, and during the past 18 months a new concept of the importance of the adrenal cortex has been recognized. The end of this new chapter is not yet in sight, but as speculation has been replaced by factual observations the results have been no less than astonishing.

The key which has unlocked this flood of new knowledge is a white crystalline compound first isolated 15 years ago and designated simply by the letter E. During the years since its isolation it has been my hope that this compound would be made available for use in clinical medicine, and, without any prescience at all but with a great deal of conviction, I have given top priority to the preparation of compound E in so far as my interest, energy and time are concerned.

This hormone of the adrenal cortex is the most complicated pharmaceutical agent which has been prepared in the laboratory. It was first necessary to discover a series of chemical reactions which could be used to arrange suitable starting material into the desired hormone. However, merely to make compound E was not the objective; it was necessary to find a method which could be used to prepare this hormone on a large scale. This was done in my laboratory in the case of one of the hormones of the adrenal cortex (compound A) in 1944, and in 1945 Merck and Co., Inc., prepared a large sample by this method (figure 1).

In the first months of 1946 this sample was tested on laboratory animals and was found to behave exactly as did compound A, separated from the adrenal cortex [3]; but when given to patients who had Addison's disease it was found to be of little value.[4] Interest in the hormones of the adrenal cortex sank to a very low level. More than one physiologist became convinced that no hormone of the adrenal cortex was of sufficient importance to justify additional work in this field, and more than one clinician lost all hope that these hormones would some day hold an important place in clinical medicine. In 1946 there was no conclusive evidence that compound E was qualitatively different from compound A, and there was therefore no assurance that large-scale production of compound E was worth while.

Under these circumstances, Merck and Co., Inc., adopted a course which was a compromise. They decided to make a small sample of compound E. An important reason for this decision was the fact that in 1946 Dr. L. H. Sarett, working in the research laboratory of Merck and Co., Inc., had prepared a few milligrams of compound E, but the yield was so small that the method he used could not be applied to large-scale production.[5]

During the following 18 months, important improvements for some of the steps in the preparation of compound A were devised in my laboratory,

and Dr. Sarett discovered an entirely new procedure to convert a product closely related to compound A into compound E by introduction of a hydroxyl group at C-17.[6] The final yield of compound E [6] was raised nearly a hundredfold.

Fig. 1. Flow sheet for the conversion of desoxycholic acid into 11-dehydrocorticosterone (compound A). Introduction of a hydroxyl group at C–17 to form cortisone requires eight additional steps.

In April, 1948, a few grams of compound E acetate were in hand, and it seemed advisable to Merck and Co., Inc., to hold a conference with a group of clinicians to consider how the material should be used. This conference marks the all-time low point in the fortunes of compound E. Some confidence in the value of compound E in the treatment of Addison's disease was expressed, but for the most part it was feared that compound E would take its place among discarded drugs, right beside compound A. No newspaper re-

porters waited for the result of the meeting, no committee was needed to allocate the very small amount of compound E which was ready for use, and Merck and Co., Inc., had decided that, unless some wide demand for compound E developed, they would not make more of this hormone.

The months from April to October, 1948, are perhaps the most interesting period in the development of the clinical application of compound E, not because of what was done but because of what was not done. The situation at that time furnishes good evidence for our lack of information concerning the function of the adrenal cortex. Had anyone suggested, during those months, that compound E should be administered to patients who had rheumatoid arthritis, he would have been asked to state the rationale for such a seemingly irrational proposal. I know this to be true from actual experience, and I also know that when Dr. Hench and I attempted to state a rationale, the result was not too impressive. Nevertheless, there was at least a theoretic basis for the suggestion that compound E might relieve the symptoms of the disease, rheumatoid arthritis.

Rheumatoid arthritis has been considered to be a relentlessly progressive disease, with death the only avenue of escape from pain and deformity, but in 1929 and 1931 Dr. Philip S. Hench made two observations which led him to believe that this disease is potentially reversible.[7] The first was that, during an attack of jaundice, the painful symptoms of rheumatoid arthritis frequently were relieved for a period which varied from a few weeks to several months or even years. The second observation was that, during the months of pregnancy, women who had arthritis frequently were relieved of symptoms of the disease.

Dr. Hench and I have had many conferences over the probable cause and treatment of rheumatoid arthritis, and at such a meeting, in January, 1941, we reached the decision that compound E should be employed for patients who had rheumatoid arthritis. The reasons why we believed that compound E should be tried have been given, and I shall not repeat them here, but it is desirable to explain why compound E was not employed until September, 1948, although compound E acetate was available as early as May of the same year.

The reason for the delay is to be found in previous experience with the acetates of compound A and compound E. It had been observed that these acetates are slowly absorbed, and it seemed doubtful that the hormone would be taken up rapidly enough for it to produce its maximal physiologic effect. But in May, 1948, the separation of compound E from its acetate had not been achieved, and a suitable procedure was not available until September, when Dr. V. R. Mattox, in my laboratory, made this operation feasible.[8]

There remains one important detail which should be mentioned: the daily dose. It is not an exaggeration to say that the successful investigation of compound E was assured when we decided to grind the crystals to a fine powder, to use 100 mg. for the daily dose, and to inject the material intra-

muscularly. This insured a slow absorption continued over many hours, a condition simulating the mode of release of the hormone from the gland. On September 21, 1948, Dr. C. H. Slocumb injected 100 mg. of compound E intramuscularly into a patient who had rheumatoid arthritis. Throughout the winter of 1948–1949, 15 more patients received the hormone, and in the spring, five patients with rheumatic fever were given compound E.

The effect of compound E on rheumatoid arthritis and rheumatic fever has been made known in medical journals, newspapers, magazines, and over the radio. Compound E and related substances have become the present delights of newspapers and publicity seekers. Most of you already know that the effect of compound E was obvious in all patients who had rheumatoid arthritis or rheumatic fever.[9] At present more than 300 such patients have received compound E and all have responded. I have not heard of a single exception.

These results in turn suggested that compound E might influence the so-called collagen diseases. Prominent among these are lupus erythematosus, psoriasis, pemphigus, and conditions associated with allergy, such as asthma and hay fever. When compound E was given to patients who had these diseases, encouraging results were obtained. Now for the first time some insight has been gained concerning the wide influence of the hormones of the adrenal cortex. The two spheres of investigation, one in clinical medicine and one in biochemistry, have been brought together. They are two aspects of one problem. Today we do not know how many more important factors remain to be identified before final solution of the problem can be accomplished, but we can visualize the outline of the problem more clearly than at any time hitherto.

The effect of compound E on rheumatoid arthritis was reported on April 20, 1949,[10] and shortly thereafter there were rumors of a sharp increase in the sale of vitamin E. One energetic company went so far as to advertise "vitamin E compound." For this reason it seemed desirable to give a distinctive name to compound E. Dr. Hench and I chose the name "cortisone," which was derived by deletion of certain letters from the formidable chemical name, 11-dehydro-17-hydroxycorticosterone.

Cortisone is a powerful tool with which it is possible to study problems related both to etiology and treatment of a large group of diseases. In due course this will be done, but at present speculation is of less value than observation, and I shall not attempt to predict the course of further investigation. However, it is helpful to consider some facts which have already been disclosed. We can now answer the question, Are rheumatoid arthritis and rheumatic fever caused by inability of the adrenal cortex to produce cortisone? The answer is, quite clearly, no. The incidence of rheumatoid arthritis and rheumatic fever is not increased among patients who have Addison's disease and, in the past, examination of patients who had rheumatoid arthritis has not revealed significant symptoms of adrenal insufficiency. Deter-

mination of the rate of excretion of 17-ketosteroids and corticosteroids has failed to show a significant decrease in the apparent functional capacity of the adrenal cortex.[11]   These results have formed a screen behind which were hidden the collagen diseases which we now know are affected by cortisone. New tools have been provided which some day may lead to a treatment and perhaps to relief for some of these who suffer from these diseases.

Does cortisone induce changes in the diseased tissues indicative of a healing process?   Examination of the synovial membranes of patients who have rheumatoid arthritis, of the bone marrow in lupus erythematosus, of the arteries of patients who have periarteritis, and of the skin of patients who have pemphigus indicates that partial but marked healing of the lesions has occurred during the administration of cortisone.   Moreover, many patients who had rheumatoid arthritis have enjoyed remissions of the disease which have lasted several months.   These results indicate that the administration of cortisone alone can restore the power of the tissues to check the advance of the disease and to initiate repair of the affected part.[9]

Does cortisone act as a general stimulus to the metabolism of foodstuffs, with an increase in the basal metabolic rate, or does it exert a special effect on one metabolic process which can explain the over-all influence of cortisone?   Cortisone does not increase the basal metabolic rate.   In amounts up to 100 mg. for a daily dose in patients without renal lesions, cortisone does not change significantly the metabolism of sodium, potassium, magnesium, calcium, phosphorus, chloride, sulfur, or nitrogen.[11]   Carefully controlled balance studies in the metabolic unit have not revealed any metabolic change which could provide the basis for an interpretation of the effect of cortisone on any of the diseases which have been studied.

Does cortisone act as a general pharmacologic agent, not in a specific way, on the diseased part?   This is more difficult to answer.   Cortisone does increase the appetite, produce a sense of well-being, and bring about a psychosomatic response which is not directly related to any particular disease.   In this respect the effect is a general one.   However, this influence of cortisone is not shared with any other known substance except the closely related compound F, another hormone of the adrenal cortex.   But in addition to the marked improvement in the psychosomatic sense, there is a selective effect of cortisone on the diseased parts which is highly specific for cortisone and compound F.   Decrease in the sedimentation rate to normal or near normal, relief from pain, and prompt arrest of the usual progress of the disease are not general pharmacologic responses.   These effects are not produced by any other of the many steroids present in the adrenal cortex, or by any other closely related compound.

There remains one other important question: What are the effects of large amounts of cortisone when it is given for a long time?   The answer to this question is not a simple one.   Age, sex and the response of each individual are important factors.   In general, however, the response to corti-

sone is neither rapid nor long continued. There is no immediate response to cortisone. It is best to employ this hormone in a form which will be absorbed over many hours and, even so, daily injections are necessary. Almost all individuals are able to receive 100 mg. of cortisone daily for a month or more without showing any undesirable effect, but when cortisone is given at a dose of 200 mg. daily some patients will exhibit changes within 10 days or two weeks. These changes have been described and will not be repeated here.[9, 11]

There are, however, two aspects which I should like to point out. The first is that all the effects of overdosage are reversible when the administration of cortisone is discontinued, and the second is that, as more is learned about the response to cortisone, it seems neither necessary nor desirable to give large daily doses for long periods. At this time, speculation on the future use of cortisone will be avoided.

Cortisone suppresses the activity of the adrenal cortex and, if administration of the hormone in large amount is long continued, atrophy of the adrenal cortex will occur. However, suppression of the functional capacity of the gland also appears to be reversible, and sudden termination of the use of cortisone is not attended with serious symptoms of adrenal insufficiency.[9]

Immediately after the announcement that cortisone relieved the symptoms of rheumatoid arthritis, there was one thought—I may even say "conviction"—which occurred to many chemists and clinicians in many different institutions. It was this: if cortisone is good for rheumatoid arthritis and rheumatic fever, there must be several other substances which are just as good or better. In the first publication, issued on April 13, 1949, there was a statement, boxed off in a wide black border, to the effect that compound E was not then available and that a year or more would have to elapse before it could be produced in significant amounts.[10]

The common reaction to this situation was to ask, Why wait a year or more? Surely something else must also be active. Long lists of steroids were made out, and intensive work was begun to make these substitutes. Many compounds closely related to cortisone have now been made and employed among patients who previously had received cortisone (figure 2). I am aware of the fact that some of these compounds have been employed for patients who had rheumatoid arthritis, and that a certain percentage of these patients have responded favorably. But it is also true that the favorable effects were not observed in more than the usual number of those who suffer from this disease and who respond to treatment with a placebo or any one of a large number of unsatisfactory remedies of the past. I have been told by Dr. Hench that as many as 30 per cent of patients who have rheumatoid arthritis temporarily respond favorably to the injection of an isotonic solution of sodium chloride. In the past this has been misleading and difficult to explain, but with the clear demonstration that slight stimulation of the adrenal cortex can bring relief to some patients who have

rheumatoid arthritis, perhaps it will be possible to explain why a goodly percentage of patients do find relief not only from injections of isotonic solution of sodium chloride but also from administration of a foreign protein, or an anesthetic agent, or from starvation or psychic stimulation. All of these changes may stimulate the adrenal cortex.
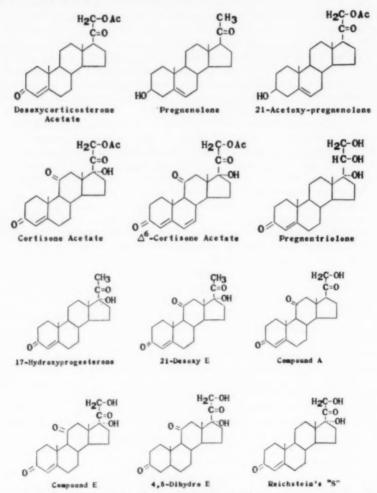
FIG. 2. Structural formulas of steroids closely related to cortisone which have been investigated for their effect on patients who have rheumatoid arthritis. Cortisone is included in the lower left corner for comparison. None of the other compounds produced the typical effects of cortisone.

Between these transient responses and the specific effect of cortisone there is a wide gulf. Cortisone has brought relief.to all patients who have rheumatoid arthritis.

In an attempt to find a substitute for cortisone, the suggestion has been made that administration of a compound closely related to cortisone would permit the body to convert the material into cortisone. This is an attractive hypothesis, and if some easily prepared compound were transformed by the body into cortisone, much of the delay and expense associated with the manufacture of cortisone would be removed.

Unfortunately, the wide divergence between the physiologic activity of cortisone and the other compounds makes it clearly evident that the tissues of the body do not have the power to elaborate cortisone from closely related compounds. The introduction of ketone or hydroxyl groups, or even a double bond at $C_4:C_5$, apparently cannot be accomplished. On the other hand, these compounds appear to be altered into some product quite different from the material which was injected. Cortisone is not excreted in significant amounts in the urine, and the same statement can be made of all the other compounds.[11]

The adrenal gland itself appears to be the workshop wherein are contained the enzymes which can elaborate the hormones of the adrenal cortex. The many steroids which are found in the gland probably are intermediate compounds which are retained within the gland and are not released until they in turn have been completely elaborated into cortisone, or closely related compound $\overset{.}{F}$. Only the finished hormones are released when the gland is stimulated.

Today cortisone is scarce, expensive and not well understood, but strong forces which will affect these problems have been set in motion and these are rapidly gaining momentum. Both in this country and abroad, pharmaceutical manufacturers, research chemists, physiologists and clinicians recognize that study of the problems associated with the adrenal cortex has a high priority, and it may well be that in the not distant future the innermost secrets of both the adrenal cortex and the collagen diseases will be revealed.

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CLINICAL RECOGNITION AND TREATMENT OF ACUTE POTASSIUM INTOXICATION *

By John P. Merrill, M.D.,† Harold D. Levine, M.D., F.A.C.P., *Boston,*
Walter Somerville, M.D.,‡ M.R.C.P., *London,* and Stephen
Smith, 3rd, M.D.,§ *Boston, Massachusetts*

The toxicity to the living organism of an excess of potassium ion in the extracellular fluid has been recognized for many years.[1, 2, 3] The accumulation of toxic amounts of potassium may occur by reason of: (1) excess intake,[2, 4, 5] (2) faulty metabolic handling,[6] and (3) decreased excretion of potassium liberated by catabolic processes.[7, 8, 9] The syndrome is encountered most frequently in clinical practice as a consequence of impaired excretion of potassium in the presence of increased mobilization or intake.

The clinical syndrome of potassium intoxication has been recognized with increasing frequency [10, 11, 12, 13, 14] and the characteristic electrocardiographic changes stressed.[7, 12, 15, 16, 17] It is the purpose of this paper to report nine cases of hyperkalemia, to stress the rôle of electrocardiographic changes in its detection and evaluation, and to discuss the therapeutic methods available.

Case Reports

Case 1. A 48 year old male was admitted October 19, 1948, with a history of recurrent joint pains of 10 years' duration, and fatigue, ankle edema, dyspnea and "dark urine" of three months' duration.

Physical examination showed slight periorbital edema and marked edema of the lower extremities. There was a harsh, grade II apical systolic murmur. Blood pressure was 142/88 mm. Hg. Urine examination revealed 3 plus protein, and many red cells and white cells in most specimens with hyaline and granular casts. Blood urea nitrogen was 55 mg./100 ml., and carbon dioxide combining power 21.1 mM/L. Chest roentgenogram showed moderate enlargement of the heart to both left and right, with fluid in both costophrenic angles. Initial electrocardiogram was normal except for low EMF.

Hospital course: The patient's hospital course was steadily downward. The urine volume after the first week was small, ranging between 150 and 940 ml. daily, with an average of about 700 ml. With this there was increasing azotemia, acidosis and accumulation of pleural fluid.

Fig. 1.

On the twenty-fifth hospital day the patient developed rapidly increasing weakness and a burning sensation in the soles of his feet. The following morning he was unable to move his arms or legs, and reflexes were noted to be absent in all extremities. He began to have difficulty in speaking and one hour later was completely aphasic, while respirations became shallow and labored. Electrocardiogram at this time showed advanced changes of potassium intoxication. Serum K was 9.8 mEq/L and serum Na 122 mEq/L.* He was treated with parenteral therapy consisting of: (1) 500 ml. of 0.9 per cent saline solution containing 75 gm. of glucose and 35 units of crystalline zinc insulin; (2) 500 ml. of 3 per cent saline solution; (3) 150 ml. of 0.9 per cent saline, and (4) 250 ml. of 5 per cent dextrose in 0.9 per cent saline, containing 5 units of crystalline zinc insulin. This treatment was administered in a 35 minute period during which, consecutively, he became able to move first his fingers and then his arms, his voice returned, respirations became normal and, finally, reflexes became obtainable in all extremities.

The patient was then run on the artificial kidney (hemodialysis), with further striking chemical and clinical improvement. The serum sodium rose from 122 mEq/L to 136 mEq/L, and serum potassium fell from 8.0 mEq/L to 5.7.

On the evening of November 16, 1949, the patient's symptoms of potassium intoxication had returned.

Inspection of the electrocardiogram at this time showed moderate changes (figure 1A). The rhythm was regular, the QRS duration 0.14 second, the R waves small, the S waves deep, the S–T segment a smooth, almost continuous slanting line, and the T waves tall and pointed. P waves could not be identified with certainty. The serum potassium level taken shortly thereafter (8 p.m.) was 10.1 mEq/L. Figure 1B shows fragments of a continuous recording of Lead II taken before, during and after the intravenous infusion of 500 ml. of a solution containing 50 grams of glucose, 20 units of crystalline zinc insulin, and 2 grams of calcium gluconate. The strips mounted were recorded at 8:00 a.m. (when the infusion was begun), 8:07, 8:20, 8:30, 8:45 (just at the conclusion of the infusion), and finally at 9:00 p.m. A striking shortening of the QRS duration (0.14 to 0.11 second) was already apparent in the tracing taken seven minutes after the beginning of the infusion, and auricular activity returned. Very little, if any, further change developed during the remainder of the infusion. Comparison of a set of nine leads taken at 9:00 a.m. (figure 1C) with that taken before the infusion (figure 1A) shows the improvement obtained much more strikingly than the continuous recordings (figure 1B) made in Lead II during the infusion. A serum potassium level was not obtained until three hours later, so that a definite statement regarding the correlation of the blood chemistry and the electrocardiogram at the completion of the infusion is not warranted.

That the electrocardiographic improvement following the glucose-insulin-calcium infusion was transitory is demonstrated in another set of tracings (figure 1D)

* All sodium and potassium values were determined by the flame photometer using the internal lithium standard. Whenever the sample was adequate, determinations were made in duplicate.

FIG. 1. *Case 1*, uremia. Partial, transitory or unsatisfactory effect of chemical treatment in hyperkalemia. (A) Control tracings showing moderate potassium poisoning. Rhythm regular. Note absent P waves, broad QRS complexes (0.14 sec.), small R, deep S, smooth S–T segments and tall pointed T waves. (B) Strip of continuous recording of Lead II in relation to infusion of mixture of glucose, insulin and calcium. Note shortening of QRS from 0.14 sec. at 8:00 to 0.11 sec. at 8:07. (C) Standard and unipolar chest leads at end of infusion showing marked electrocardiographic improvement but persistent intraventricular block and peaked T waves. (D) Complete set of tracings two hours later showing return of moderate hyperkalemic changes and demonstrating that improvement was transitory. (E) Effect of calcium gluconate intravenously shortening QRS from 0.14 to 0.12 sec., P–R unchanged. (F) Lack of effect of glucose solution alone.
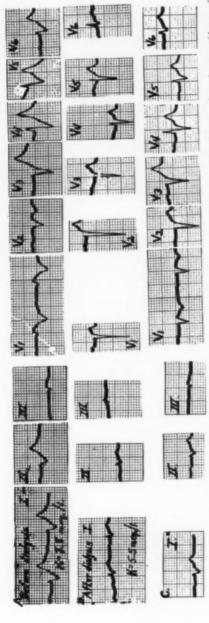
Fig. 2. *Case 1* (continued). Persistent and maximal effect of hemodialysis in hyperkalemia. (A) Return of moderate evidence of potassium poisoning six hours later. P–R 0.28 sec., serum potassium 8.8 mEq/L. (B) Following artificial kidney, normal tracings except for low EMF, serum potassium 5.5 mEq/L. (C) Tracings taken three days later showing only slight regression (P–R 0.28 sec., QRS 0.11 sec.) indicating relative persistency of improvement.

taken two hours later (P–R interval 0.28 second, QRS duration 0.14 second). It was then decided to test the individual effect of the various components of the mixture which had previously shortened auriculo-ventricular and intraventricular conductions. Accordingly, at 11:53, 20 ml. of 10 per cent calcium gluconate solution alone was slowly injected by vein. Figure 1E shows Lead II before the infusion, after 2 c.c. and after 10 c.c. had been run in. A slight shortening of the QRS interval from 0.14 to 0.12 was noted but the P–R interval remained unchanged at 0.24 second. One hundred ml. of 10 per cent glucose in water was then infused from 12:10 to 12:23 a.m. (figure 1F) without further electrocardiographic effect. Neither solution produced any change in the serum potassium level.

Later that morning (November 17), at 7:45 a.m., the electrocardiogram showed more advanced changes of potassium intoxication. The P–R interval was 0.28 second and the QRS duration 0.16 second (figure 2A). It is apparent, then, that what little improvement had been obtained by the use of this intravenous therapy was short-lived, characteristic changes recurring within six hours. At 11:30 a.m. the serum potassium level was 8.8 mEq/L. Then, for the second time in this patient, hemodialysis with the artificial kidney was started and continued for three and one-half hours. At 4:15 p.m. the serum potassium level had fallen to 5.5 mEq/L and the electrocardiogram (figure 2B), except for low voltage in the limb leads, had become quite normal. The P–R interval had shortened to 0.20 second and the QRS duration to 0.07 second. It became apparent then that the artificial kidney, with its ability to withdraw potassium from the serum, produced a return to normal electrocardiographic complexes when the chemical procedures enumerated were able to produce only partial and very transient electrocardiographic effects. The relative persistency of the changes produced by the artificial kidney is demonstrated in the set of tracings (figure 2C) taken three days later. They showed only slight changes (P–R interval 0.28 second, QRS duration 0.11 second), and contrast vividly with those recorded just before hemodialysis.

Following this episode the patient ran an irregular fever and continued to be oliguric. On the thirty-fourth hospital day the clinical signs of marked potassium intoxication returned, the electrocardiogram again showing the previously described changes, which progressed to ventricular fibrillation immediately before death. Post-mortem examination revealed subacute bacterial endocarditis with a focal embolic glomerulonephritis.

Case 2. A 35 year old Italian housewife was admitted for the first time because of anuria of three days' duration. Four days before admission, in the eighth month of her pregnancy, she had noted vaginal bleeding associated with low abdominal pain. Three days before admission she was admitted to another hospital, where blood pressure and urine were found to be normal. At that time a low vertical Caesarian section was performed and the patient delivered of a viable infant. During the procedure, however, the patient went into shock and received 1,500 ml. of type O, Rh positive blood, which was subsequently shown to be completely compatible. The following day the patient voided less than 200 ml. of grossly bloody urine and, because of persistent oliguria and increasing azotemia, was transferred to this hospital.

Physical examination on admission disclosed a somewhat obese, apprehensive woman, who appeared quite alert. The lungs were clear, blood pressure was 108/62 mm.Hg, and the heart was negative except for a grade II systolic murmur at the left sternal border. Liver and spleen were not felt. There was one plus pitting edema of the ankles and sacrum. Tendon reflexes were generally hyperactive and equal, with the exception of the ankle jerks, which were not elicited.

Laboratory data: One ml. of urine obtained on admission showed 4 to 6 red blood cells and many white cells in the sediment. Hematocrit was 24; white blood

cell count 6,850. Blood urea nitrogen was 59 mg./100 ml., serum carbon dioxide combining power, 18.4 mM/L and serum chlorides, 83 mEq/L.
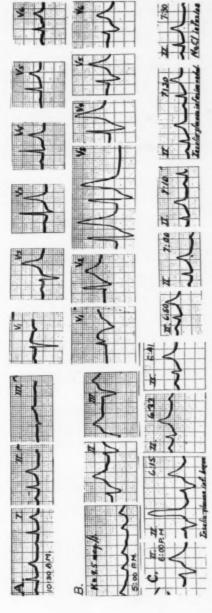
Hospital course: At first the patient appeared to be doing quite well on a regime of restricted fluid intake and intravenous glucose infusions. The first tracing (figure 3A), recorded between 10 and 11 a.m. on the second hospital day, when the clinical diagnosis of potassium intoxication had not yet been made, showed tall pointed T waves. T_2 was slightly taller than R_2, and first degree heart block was present. In view of these findings, the possibility of potassium intoxication was suggested. During the day the patient became lethargic and complained of pain in the back, and at about 4 p.m. was unable to move her legs. Over the course of the next hour she became progressively weaker. She was unable to perform any gross movements of her extremities, although she could move her toes and fingers slightly. Her voice became progressively weaker and by 5:15 she could speak only in a whisper. At this point a second set of tracings was obtained (figure 3B). This showed much more pronounced changes (decreased height of the R waves, increased depth of the S waves, first degree heart block, intraventricular block, irregular cardiac rhythm apparently due to sinus arrhythmia, smooth slanting S–T segments and tall narrow pointed T waves, most pronounced in leads $V_{3 and 4}$. The diagnosis of potassium intoxication was made and was confirmed later when the report of the blood chemistries revealed a serum potassium level of 9.5 mEq/L.

In order to combat hyperkalemia until hemodialysis could be undertaken, the patient was then given 70 grams of glucose with 35 units of crystalline zinc insulin in 300 ml. of water, and a continuous recording was made of Lead II with the direct writing electrocardiograph (figure 3C). A control recording at 6 p.m. showed no recognizable P waves; the QRS duration was 0.20 second, the R wave small and the S wave deep. At this time the patient's tendon reflexes were absent. The infusion was started at 6:15 p.m. and completed at 7:20 p.m. A progressive shortening of the P–R and QRS intervals, increase in the height of the R waves, and decrease in the depth of the S waves were apparent during the course of the infusion. The tracings obtained after the completion of this part of the infusion showed the QRS duration to be 0.08 second, but the P–R interval was still slightly prolonged (0.22 second) and the T wave still slightly taller than the R wave. At 6:45 the patient was able to speak aloud again and the left biceps jerk could be elicited. At 7:00 she could grip with her hand, and at 7:20 all of the tendon reflexes were present but hypoactive. At 7:25 a blood sample was obtained for potassium determination but unfortunately was destroyed by accident. From 7:25 to 7:30 100 ml. of 3 per cent sodium chloride was given by vein, producing no further clearcut change in the appearance of the tracings.

A complete set of tracings (figure 4A), taken at 8:45 p.m., when the serum potassium level was 9.1 mEq/L, showed Lead II much as it was following the infusions. The T waves were tall, narrow, and pointed in leads V_{2-4}. Hemodialysis with the artificial kidney was begun at 10:45 p.m. and completed at 6 a.m. the following morning. Electrocardiograms taken an hour later (figure 4B) showed that these tall T waves had become considerably shorter but were still taller than normal. The serum potassium level was now 6.0 mEq/L and the sodium 132 mEq/L. On the following day, without further treatment, the tracings had become quite normal in appearance, the T waves no longer being pointed and the R waves having a normal amplitude.

Four days following dialysis, though the serum potassium had increased to much higher levels (8.3 mEq/L), the only electrocardiographic change was the presence of tall T waves in the precordial leads (figure 4C). At this time the serum sodium was 139 mEq/L. Although there was some tendency, from the electrocardiographic and clinical standpoints, to persistent hyperkalemia, the patient showed a slow pro-

Fig. 3. *Case 2.* Anuria following premature separation of placenta. Evolution from slight to moderate evidences of potassium poisoning and salutary effect of glucose-insulin. (A) Initial curves showing first degree auriculo-ventricular block and peaked T waves, early evidences of potassium intoxication. Knee jerks absent. (B) Pronounced changes when almost completely paralyzed (decreased R, increased S, first degree block, intraventricular block, peaked T waves, prolonged Q-T interval and irregular rhythm). (C) Fragments of continuous tracing of Lead II during infusion of insulin-glucose. Note reappearance of P waves, increased height of R, decreased height of T, decreased depth of S, disappearance of intraventricular block. Paralysis largely gone. No further change from 3 grams sodium chloride.
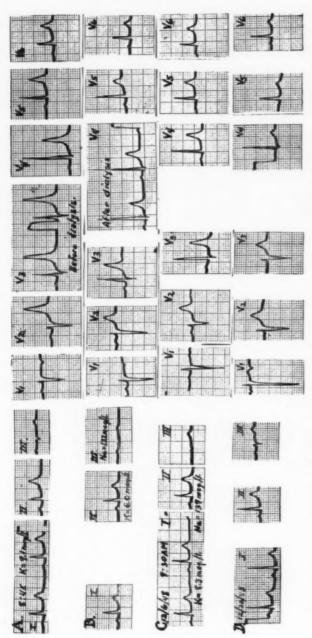
Fig. 4. *Case 2* (continued). Lack of correlation between electrocardiogram and serum potassium level. (A) Tracings taken before hemodialysis. Note very slight electrocardiographic changes (peaked T waves) despite high serum potassium level (9.1 mEq/L.). (B) Tracings following hemodialysis showing some pointing of T waves, otherwise normal curves, when potassium had fallen to 6.0 mEq/L. (C) Failure of electrocardiogram to become more abnormal despite re-elevation of potassium to 8.3 mEq/L, explicable by concomitant rise of serum sodium to normal. (D) Normal electrocardiograms recorded at time of discharge of patient.

gressive improvement with increasing urine volumes and at the time of discharge on December 20 the electrocardiogram was normal in all respects (figure 4D), and the serum potassium level was 4.7 mEq/L.

Case 3. A 68 year old man was admitted to the Peter Bent Brigham Hospital on June 29, 1949, because of a hemolytic reaction and renal shutdown following a transurethral prostatic resection.

A series of four daily electrocardiograms (Leads I, II, III and 4F only) was recorded at an outside hospital. Although none of these showed decisive evidence for hyperkalemia, a progressive increase in the height and sharpening of the T wave was apparent in the series. Figure 5A is the fourth of this outside series.

Physical examination on admission to this hospital showed a cachectic, acutely ill man, who was drowsy and responded very slowly to questioning. The lungs were clear. Blood pressure was 170/90 mm. Hg, the heart rhythm was rapid and regular, with a loud apical diastolic gallop, and a grade I aortic systolic murmur was present. Tendon reflexes were diminished generally, and no biceps, knee, or ankle jerks were elicited.

Laboratory data: Urine had a specific gravity of 1.005, pH of 7.0. There was one plus proteinuria, and the spun sediment contained 5 to 7 red blood cells and numerous white blood cells per high power field. Hematocrit was 34 and white blood count 10,300. Blood urea nitrogen was 92 mg./100 ml., carbon dioxide combining power, 15.8 mM/L, and serum chloride, 89 mEq/L.

Hospital course: Within a few hours after admission the patient appeared obviously worse, and reflexes were totally unobtainable. Because of clinical and electrocardiographic evidence the diagnosis of acute potassium intoxication was made and therapy was begun. An electrocardiogram (figure 5B) recorded shortly after admission and on the ninth day of anuria showed regular rhythm, widening of the QRS complexes, tall, pointed T waves in leads V_{2-4}, the ascending limb of the T wave being almost in direct continuity with the ascending limb of the S wave and the beginning of the T wave appearing to merge with the end of the QRS complex. P waves could not be recognized. Because of the difficulty in defining the end of the T wave, the Q–T interval was not measured but was obviously increased. The serum sodium at this time was 120 and the serum potassium 9.5 mEq/L.

Tracings obtained after the intravenous injection of 4 grams of calcium gluconate (figure 5C) revealed no significant change. The sodium remained at 121 and the potassium fell to 8.5 mEq/L. Neither intravenous injection of sodium chloride (2.75 grams) (figure 5D) nor of sodium bicarbonate (3.5 grams) (figure 5E) had any effect on the electrocardiogram, although at the completion of the latter infusion the patient, who had heretofore been semi-stuporous, became somewhat more alert and able to answer questions hesitantly. This clinical improvement was of less than 15 minutes' duration. The serum sodium concentration remained unchanged at 121 mEq/L despite these several procedures, while the serum potassium showed a slight increase to 9.0 mEq/L.

An electrocardiogram taken after the intravenous infusion of a solution of glucose (50 grams) and crystalline zinc insulin (25 units) is reproduced in figure 5F and, for the first time, showed a ventricular arrhythmia. The QRS duration had shortened to 0.13 second. Serial tracings taken while additional glucose and insulin were being administered intravenously showed a progressive shortening of the QRS duration; when 100 grams of glucose and 50 units of insulin had been given this interval was 0.10 second (figure 5G), but the ventricular arrhythmia was still present. The T waves in the precordial leads had diminished in amplitude but were still abnormally tall and pointed, while electrical systole had decreased (K = 0.43). The patient's clinical condition was now considerably improved and the superficial and deep reflexes, previously unobtainable, could now be elicited. The serum sodium

had risen to 127.5 mEq/L but the potassium was still elevated (8.2 mEq/L). The patient was then run on the artificial kidney with further chemical and clinical improvement.

Electrocardiograms taken in the course of hemodialysis revealed a continuous reversion toward the pattern normal for the patient. After two and a half hours of

FIG. 5. *Case 3.* Ineffectiveness of calcium and sodium salts and effectiveness of glucose-insulin and hemo-dialysis in potassium poisoning. (A) Outside tracings showing pointed T_{IVF} of doubtful significance. (B) Tracings taken on admission characteristic of potassium poisoning (widened QRS, peaked T waves, sloping S–T segments). P waves not recognized. Rhythm regular, rate 115). (C) Failure of electrocardiogram to improve following calcium. (D) Same following sodium chloride. (E) Same following sodium bicarbonate. (F) Improvement (shortening of QRS to 0.13 second) but persistence of S–T depression, peaked T waves, absent P waves and inception of ventricular irregularity following glucose-insulin. (G) Further improvement (QRS shortened to 0.10 second, T waves smaller) following further administration of glucose-insulin. (H) Normal electrocardiograms following hemodialysis.

dialysis, when the serum sodium was 127.5 and the serum potassium 5.0 mEq/L, the tracing (figure 5H) was normal, the rhythm having become regular and the P waves having returned. The following day 735 ml. of urine were passed and with the onset of diuresis, recovery was gradual until discharge on the twenty-eighth hospital day.

Case 4. A 35 year old housewife was admitted to the Peter Bent Brigham Hospital with a history of oliguria of eight days' duration which followed the delivery
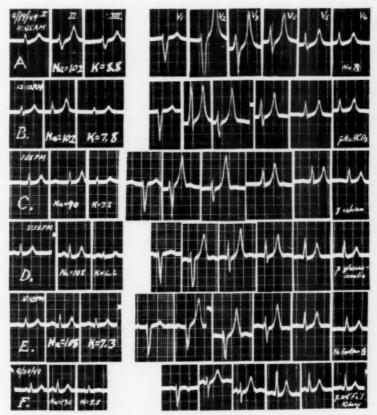
Fig. 6. *Case 4.* Postpartum oliguria. Incomplete effectiveness of chemotherapy contrasted with virtually complete effectiveness of hemodialysis. (A) Tracing on admission showing moderate electrocardiographic changes (peaked T waves, prolonged Q–T interval, increased QRS, absent P waves). Ventricular arrhythmia, not shown here. (B) Slight improvement following sodium bicarbonate (normal QRS, sporadic low-voltage P waves associated with persistence of ventricular irregularity). (C) Further improvement following calcium (P waves more prominent, Q–T interval normal, first degree auriculo-ventricular block now apparent). Note appearance of U waves. (D) Following glucose-insulin, normal electrocardiogram except for peaked T waves. (E) Following temporary cessation of therapy, marked clinical and slight electrocardiographic regression (sinus arrhythmia, broader P waves, minimally depressed S–Tᵥ₊₋). (F) Following hemodialysis normal tracings showing possible peaking of T waves as sole change.

of a child nine days before admission. She had developed hypertension and seven hours after delivery had had a generalized convulsion followed by nine more convulsions at hourly intervals. For the next eight days the urine output averaged 60 ml. per day.

Physical examination showed a pale, lethargic woman with ecchymoses on the shoulders and cheeks. There were moist, crackling râles up to the scapula over the left lung field posteriorly. The right lung field was clear. The liver was enlarged five fingers'-breadth below the right costal margin. Blood urea nitrogen was 81 mg. per 100 ml., carbon dioxide combining power 15.4 mM per liter, serum chloride 69 mEq/L.

The first electrocardiogram (figure 6A) was characteristic of potassium intoxication, with abnormalities including complete absence of P waves, prolonged Q–T interval and transient arrhythmias. In lead V_6 the rate varied from 30 to 70 beats to the minute. Short runs of premature ventricular beats were recorded. At this time the serum sodium level was 102 mEq/L and the serum potassium 8.8 mEq/L. The patient was in coma.

Figure 6B illustrates the electrocardiogram after the intravenous administration of sodium bicarbonate (3.75 gm.) in 300 ml. of 5 per cent glucose solution. The QRS had shortened to 0.10 second and the return of auricular activity was indicated by sporadic low P waves. The ventricular rhythm was irregular. The sodium and potassium levels were 102 mEq/L and 7.8 mEq/L, respectively, and the patient was becoming responsive. The clinical improvement was of short duration, however, and the patient regressed in 10 minutes to her pre-infusion status. None of the tendon reflexes could be elicited. Repeated estimation of the serum sodium and potassium values demonstrated that the serum sodium was little changed (one value of 90 mEq/L is to be questioned), while the serum potassium remained at a constant value (7.8 mEq/L). Slight clinical improvement was noted in the patient, but she was still semi-comatose and the tendon reflexes were absent.

Intravenous calcium gluconate (2.0 grams in 100 ml. of 5 per cent glucose solution) was now given and the electrocardiogram (figure 6C) showed more prominent P waves, but the ventricular rhythm was still irregular and there was no apparent temporal relationship between P and QRS complexes. The Q–T interval was now within normal limits.

Glucose (50 grams) and crystalline zinc insulin (30 units) were now given intravenously. The rhythm became regular (figure 6D) and, apart from abnormally tall and pointed T waves, the electrocardiogram was within normal limits. Prominent upright U waves were noted in leads V_{1-4}. There was marked clinical improvement, the patient becoming responsive and the tendon reflexes being readily obtained. Sodium and potassium values were 108 mEq/L and 6.6 mEq/L, respectively. In the next one and one-half hours, while the artificial kidney was being readied, the patient gradually became semi-stuporous, the pulse irregular and the reflexes sluggish. The electrocardiogram (figure 6E) showed slight regression with sinus arrhythmia and slight S–T segment changes (V_6) resembling those seen in the earlier tracings. The T waves were still abnormally tall and pointed. The serum sodium was unchanged (108 mEq/L), but the serum potassium had increased to 7.3 mEq/L.

Hemodialysis by means of the artificial kidney was begun, and after six hours a marked improvement in the clinical condition was apparent, the patient being now fully alert, the pulse regular and the reflexes normal. The serum sodium had increased to 130 mEq/L and the serum potassium had fallen to 5.5 mEq/L. The T waves, especially over the left side of the precordium, were lower than heretofore but still showed a tendency to be pointed (figure 6F). Otherwise the tracing was normal.

The following day 2,650 ml. of urine were passed with subsequent continuance

of diuresis. There was gradual but definite daily improvement in the clinical and chemical status until discharge on the twenty-first hospital day.

Case 5. A 35 year old housewife was delivered six days before admission of a stillborn fetus following three eclamptic convulsions. Since that time the urinary output had ranged between 30 and 60 ml. a day.
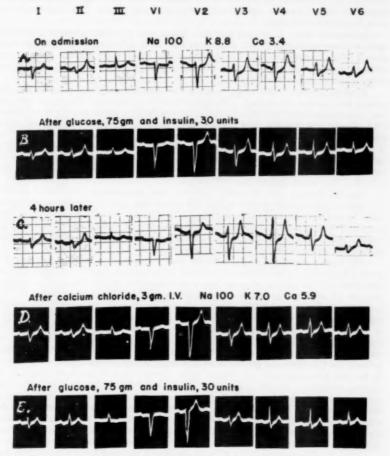
Fig. 7. *Case 5.* Anuria associated with eclampsia. Transient effectiveness of parenteral therapy in potassium poisoning. (A) Tracings on admission highly suggestive of potassium poisoning (low EMF, P–R 0.22 sec., QRS 0.12 sec., depressed S–T segments, peaked T waves, prolonged Q–T interval). (B) Marked improvement following glucose-insulin (QRS normal, T waves less pointed, S–T segments less depressed, Q–T shortened, P–R interval still prolonged). Note appearance of U waves. (C) Return of abnormal electrocardiogram after lapse of four hours without treatment. (D) Improvement similar to that noted in B following calcium therapy. (E) Further improvement following subsequent glucose-insulin (low EMF and possibly pointed T waves only residual changes).

Physical examination revealed a weak, somewhat lethargic woman complaining of pain over the lower back. There were diffuse ecchymoses over both arms and mild icterus of the sclerae. The lungs were clear, but there was one plus edema of the sacrum. Blood pressure was 130/85 mm. Hg. The heart was not enlarged, the rate was regular at 84, and there was a grade II apical systolic murmur. The abdomen was distended, but peristalsis was normal. The liver edge was palpable one finger's-breadth below the right costal margin and was tender. All tendon reflexes were hyperactive and equal.

Laboratory data: Urine pH was 6.5. There was two plus proteinuria and the spun sediment contained 25 red blood cells and 10 to 12 white blood cells per high power field. Hematocrit was 44 and the white blood count 29,000. Blood urea nitrogen was 76 mg./100 ml, carbon dioxide combining power 13 mM/L, and serum chloride concentration 81 mEq/L.

Hospital course: Within five hours of the admission physical examination, the patient had become increasingly lethargic, markedly weaker, and the tendon reflexes had become generally hypoactive. An electrocardiogram taken at this time (figure 7A) showed low voltage, first degree heart block (PR = 0.22 second), intraventricular block (QRS = 0.12 second), and prolonged QT interval (K = 0.57). The T waves were abnormally pointed and tall and the ST segments depressed, especially in the precordial leads. The findings were considered to be highly suggestive of hyperkalemia, and the diagnosis was confirmed by a serum potassium level of 8.8 mEq/L. The serum sodium was 100 mEq/L.

Specific therapy was obviously indicated, and intravenous infusion of glucose (75 grams) and crystalline zinc insulin (30 units) was given. An electrocardiogram taken toward the end of the infusion (figure 7B) showed less ST depression and less pointed T waves, while the QRS interval had shortened to 0.10 second and the QT interval had also diminished (K = 0.49). First degree heart block persisted. Serum sodium and potassium levels were not determined.

No further treatment was given until four hours later, when the electrocardiogram (figure 7C) again displayed signs of hyperkalemia similar to those seen on admission and the patient relapsed into a semi-stuporous state. Intravenous calcium chloride (3 grams) was followed by shortening of the QRS to 0.10 second, but the low voltage in the limb leads and first degree heart block remained. Abnormally tall and pointed T waves persisted but were considerably less marked (figure 7D). A gallop rhythm previously present disappeared, and the systolic blood pressure increased from 120 to 200 mm. of mercury. Further reversion toward a normal electrocardiogram occurred after 75 grams of glucose and 30 units of insulin were infused, the PR, QRS and QT intervals now being within normal limits. The voltage in the limb leads remained low (figure 7E). There was a slight improvement in the clinical condition. At this point dialysis with the artificial kidney was undertaken for five hours, producing a marked chemical and clinical improvement, with a return of tendon reflexes. The electrocardiogram returned to normal. On the third day after dialysis the urine volume was 100 ml. in 24 hours. There was progressive diuresis, with accompanying chemical and clinical improvement, and the patient was discharged for further convalescence on the twenty-first hospital day.

Case 6. The patient was a 43 year old Negro admitted from a psychiatric hospital because of oliguria and coma. Beyond a history of recent acute alcoholic excess and some years of nocturia, the details of the present illness were unobtainable. He had passed only a few ounces of urine during the 24 hours prior to admission and in that time his fluid intake was unknown.
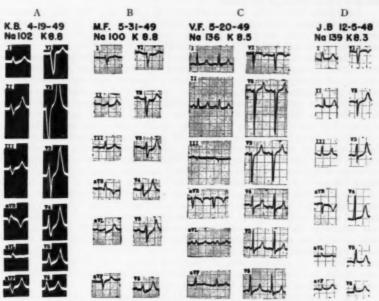
Physical examination showed a semi-stuporous man responding poorly to stimuli. Blood pressure was 109/90 mm. Hg. There was evidence of severe dehydration. The lungs were clear and the abdomen was negative. There was a grade II rough

systolic murmur maximal in the fourth left interspace at the sternal border.   No deep tendon reflexes were obtainable, and the Chvostek sign was present.

Laboratory data: Urine pH was 4.5, with a specific gravity of 1.018 and two plus protein.   There were 6–7 white blood cells per high power field and casts in the spun sediment.   Blood urea nitrogen was 93 mg./100 ml., carbon dioxide combining power 13.7 mM/L, serum chloride 112 mEq/L, and serum calcium 4.4 mEq/L.

Hospital course: An electrocardiogram taken on admission (figure 8C) showed T waves which were normal in amplitude but pointed in Leads I, II and V₂₋₄.   The S–T segments in the precordial leads slanted upward toward the T waves in a fashion previously seen in association with hyperkalemia.   The Q–T interval was within

Effect of serum electrolyte imbalance on the electrocardiogram

FIG. 8.   Effect of low serum sodium in enhancing electrocardiographic effect of high blood potassium level.   Note that the two electrocardiograms with low serum sodiums (Case 4 and Case 5) on the left show more pronounced changes than the two on the right (Case 6 and Case 2) with virtually normal serum sodium levels.   The serum potassium level in all four cases was at about the same level when these tracings were recorded.

normal limits.   The serum sodium drawn at the time this tracing was made w s 136 mEq/L and serum potassium 8.5 mEq/L.

Following intravenous therapy with glucose crystalline zinc insulin, vitamin B and calcium gluconate, there was general clinical improvement.   An electrocardiogram taken on the following day showed disappearance of the S–T segment changes and less pointed T waves.   The Q–T interval, however, had increased slightly.   The serum potassium had fallen to 6 mEq/L.   Serum sodium and calcium were not determined.

The urine volume the day after admission was 2,050 ml. Dehydration was cor-

rected with large amounts of oral and intravenous fluids, supplemented by sodium chloride and bicarbonate, with rapid clinical and chemical improvement, although there was some evidence of renal impairment as indicated by inability to concentrate. He was discharged on the eighteenth hospital day.

Case 7. This 65 year old male with chronic glomerulonephritis and pyelonephritis and benign hypertrophy of the prostate was admitted in acute urinary retention and uremia.

Physical examination disclosed a pale, drowsy, elderly man. There were a few basal râles over both lung fields posteriorly. Blood pressure was 130/80 mm. Hg. The heart was normal. The prostate was enlarged to twice normal size and there was two plus pitting edema of the ankles.

Laboratory data: Urine specific gravity was 1.004, with four plus proteinuria. The spun sediment contained 10 to 20 red blood cells and 30 to 40 white blood cells per high power field. Blood urea nitrogen was 69 mg. per 100 ml. Carbon dioxide combining power was 12.9 mM/L, and serum chloride was 94 mEq/L.

Hospital course: Throughout his hospital stay he remained in severe acidosis and uremia. Dialysis by the artificial kidney on two occasions was followed by clinical and chemical improvement, but with subsequent slow regression. On the twenty-sixth hospital day, in an attempt to rid him of edema fluid, 50 grams of a cation exchange resin which had been pre-saturated with potassium was administered by mouth. The following day the patient was noted to be weak, and that evening he was unable to move his arms or legs and no reflexes could be obtained. The electrocardiogram showed the typical changes of potassium intoxication (figure 9A). Serum sodium at this time was 112 mEq/L and serum potassium 11.5 mEq/L. It was the feeling that in this patient, whose urinary output had been good, the sudden exchange of potassium for sodium had precipitated the clinical situation. He was thus given over a three-hour period 700 ml. of 5 per cent dextrose in water, containing 7.5 gm. of sodium bicarbonate. There was marked electrocardiographic improvement (figure 9B). The serum sodium rose to 134 mEq/L and the serum potassium dropped to 9.0 mEq/L. While, unfortunately, the interpretation of the sodium effect was clouded by the concomitant administration of glucose in the solution, there is little question but that the sodium effect here was most important, since the effect of the glucose alone had not produced such marked changes (Case 1). Thus it was not until after the administration of 50 gm. of glucose with 25 units of crystalline zinc insulin that the electrocardiogram resumed the appearance it had before the onset of potassium intoxication (figure 9C).

The patient's course was progressively downward, however, and complicated by the development of staphylococcemia with multiple subcutaneous abscesses. About four hours prior to death he developed hypotension and bradycardia.

Autopsy revealed chronic pyelonephritis and generalized arteriosclerosis.

*Case 8.** This 25 year old male was found at operation in November, 1948, to have coarctation of the aorta. No repair was attempted due to the length of the constriction. He reëntered for resection with placement of an arterial graft.

Physical examination showed findings consistent with coarctation of the aorta.

Laboratory data: The urine was negative. Serum nonprotein nitrogen was 35 mg./100 ml. The electrocardiogram was interpreted as showing evidence of definite ventricular hypertrophy (figure 10A).

Hospital course: The patient was operated on on January 16, 1950, at which time, under extremely difficult conditions, a graft was placed. Blood loss was severe, requiring 14,710 ml. of bank blood for replacement. The last 14 units were so urgently needed that only repeat typing without cross match was done before administration. On later cross match all were shown to be compatible, but it was felt

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* The authors are indebted to Dr. Robert W. Gross for permission to publish this case.
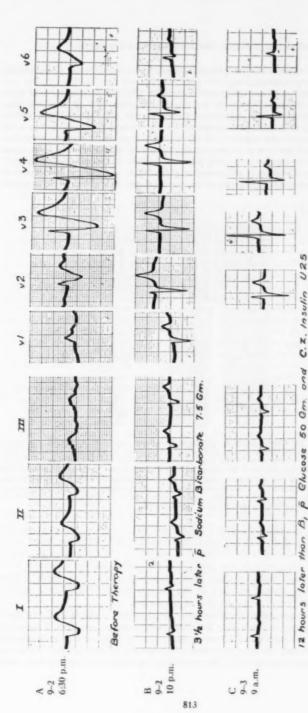
FIG. 9. *Case 11.* Hyperkalemia developing following exchange resin therapy. Partial improvement following sodium bicarbonate, complete electrocardiographic restitution following glucose-insulin. (A) Typical changes of potassium intoxication following exchange resins. (B) Shortening of QRS complex and less depression RS-T segments following 1.9 grams sodium bicarbonate. (C) Tracings following glucose-insulin-sodium bicarbonate showing restoration of electrocardiographic appearance (low voltage in limb leads and non-specific T wave changes) noted before potassium intoxication.

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that the factor of dilution in the post-transfusion blood would have decreased the chance of identifying incompatibility.

Postoperatively he showed moderate hypotension (85/60) without signs of shock and was oliguric, passing 120 ml. on the day of operation, 105 ml. the first post-operative day, 113 ml. on the second and 13 ml. on the third day. Urine specific gravity was 1.022, with four plus proteinuria. The sediment showed a few white blood cells, many casts, and crenated red blood cells. Nonprotein nitrogen rose from 46.8 mg./100 ml. on the first postoperative day to 107 on the third day, when serum pH was 7.27, carbon dioxide combining power 29 mM/L, serum chloride 74 mEq/L. Serum sodium was 129 mEq/L and potassium 8.5 mEq/L, and the hematocrit was 34 per cent. EKG taken on the morning of the day of death, on the fourth postoperative
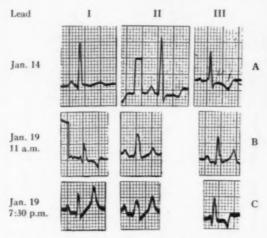
Fig. 10. *Case 8.* Lower nephron syndrome following successful repair of coarctation of aorta. Regression of characteristic changes of ventricular hypertrophy signalling early hyperkalemia. (A) Preoperative three lead electrocardiogram characteristic of ventricular hypertrophy. (B) Disappearance of changes of hypertrophy on fourth postoperative day. Variations of this type are not uncommon in hospitalized patients with ventricular hypertrophy. (C) Development of characteristic changes of hyperkalemia eight and one-half hours later and two hours before death. In retrospect curve B probably represented the earliest electrocardiographic manifestation of hyperkalemia.

day (figure 10B), showed notched $R_{1, 2, 3}$ and sharp T_3 inversion with a disappearance of the characteristic changes of left ventricular hypertrophy. EKG two hours before death (figure 10C) showed wide notched $R_{2, 3}$, low $P_{1, 2, 3}$, and tall peaked $T_{1, 2}$ with a sloping segment. No areflexia was noted, but the patient became extremely weak and apprehensive, and within a short period stuporous; then death ensued. Post-mortem examination showed changes in the kidneys typical of the lower nephron syndrome and a successful surgical repair of the aorta.

Electrocardiograms taken preoperatively, the morning of death, and two hours before death are shown in figure 10. The first tracing shows no evidence of potassium intoxication, and the second would not be suspicious in itself were it not compared with the previous one. It is evident that in the second set the inverted T_3 is now upright and slightly pointed. The electrocardiogram taken two hours before death

(figure 10C) shows further characteristic changes and, coupled with the clinical and postmortem findings, leaves little doubt that death in this case was due to potassium intoxication. The high carbon dioxide combining power was misleading, since such a finding is to be expected in a patient who had had large amounts of sodium citrate administered with the massive transfusions. However, the shallow respirations secondary to the chest wound in all probability resulted in a respiratory acidosis, a fact which is confirmed by the low serum pH. Acidosis and the possible release of potassium from hemolyzed blood are factors predisposing to potassium intoxication. This case, in which the renal lesion was reversible, emphasizes the necessity for proper evaluation of the factors predisposing to potassium intoxication and, in particular, the necessity for the comparison of serial electrocardiograms in following such a patient.

Case 9. This 16 year old male was admitted to an outside hospital following a subarachnoid hemorrhage spontaneously incurred during exercise. On admission (December 27, 1949), he was found to have a blood pressure of 194/80 mm. of mercury and signs compatible with coarctation of the aorta. After recovery from the initial episode, excision of the coarctation was accomplished on January 31, 1950. There was a moderate amount of bleeding and both bank blood and autotransfusion from the wound area were used to replace blood loss. Following operation his daily urine volume never exceeded 125 ml. for seven days, and for two days he was totally anuric. He was treated with hypertonic glucose and small transfusions. His blood pressure decreased to normal levels for the first two days postoperatively but began to rise subsequently. Femoral pulses remained easily palpable, however. Following operation he developed signs of fluid in the left chest and a large subcutaneous hematoma in the left chest wall. Serum nonprotein nitrogen was 82 mg./100 ml. on the second postoperative day and had risen to 225 on the seventh day. Serum chlorides varied between 79 and 82 mEq/L, and serum carbon dioxide combining power ranged from 35 to 40 mM/L. Daily electrocardiograms showed no essential change until the sixth postoperative day, when high pointed T waves and prolongation of the Q–T interval became evident. During this period the patient showed increasing restlessness and twitching and, following a convulsion, on the seventh day was transferred to this hospital.

Physical examination showed a restless, semi-comatose young male with frequent involuntary spasmodic jerks. Blood pressure was 220/135 mm. of mercury. The fundi showed mild papilledema with hemorrhages in the left fundus. The left chest showed signs of fluid, and a pleuropericardial friction rub was heard. There was a large subcutaneous hematoma about the wound in the left thorax. Tendon reflexes were present but slightly hypoactive.

Laboratory data: The urine was wine colored, pH was 7.0, with four plus proteinuria. The sediment contained many red blood cells and 15 white cells per high power field. Serum nonprotein nitrogen was 336 mg. per cent, blood urea nitrogen 102 mg. per cent. Serum chlorides were 83 mEq/L and carbon dioxide combining power was 21.2 mM/L. The electrocardiogram was interpreted as showing moderate changes of potassium intoxication.

Hospital course: During the night of admission the patient was treated with parenteral therapy in an effort to prevent progression of the signs of potassium intoxication. There was very little change in the clinical status or electrocardiogram. On the next morning the patient was placed on the artificial kidney with dramatic improvement both clinically and in the electrocardiogram. Blood urea nitrogen fell from 102 mg. per cent to 57, and nonprotein nitrogen from 336 to 119 mg. per cent. He was then maintained on a high caloric, low protein diet, with fluid restriction. Both clinical and electrocardiographic improvement was maintained. His urine volume reached a high of 210 ml. on the tenth postoperative day. How-

ever, he died suddenly on the morning of the eleventh day. The final episode took place in a matter of 30 seconds from his first complaint of substernal pain. The left shoulder was thrown up and the head inclined to the right. After death both pleural cavities percussed solid, and it was the feeling that the suture line in the aorta had ruptured under the continued hypertension. Permission for autopsy was not obtained.

Figure 11 shows segments of Lead II taken before and during parenteral therapy prior to hemodialysis. There is little change between the pre-infusion tracing and

	Control	p Ca	p glucose and insulin	immediately p dialysis	3 days p dialysis
Lead II					
No	133	132	135	140	138
K	8.5	8.5	8.9	7.0	7.5
Ca	4.0	6.8	3.9	4.2	3.8
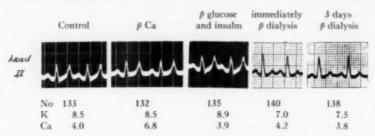
FIG. 11. *Case 9.* Failure of parenteral therapy and persistent effectiveness of hemodialysis. Postoperative and post-transfusion anuria. Serial recordings of standard Lead II. Note failure of calcium to improve electrocardiogram despite attainment of serum calcium level of 6.8 mEq/L. Dialysis effected the development of a normal serum sodium level and normal electrocardiogram despite persistent elevation of serum potassium level.

those taken after the infusion of 4 grams of calcium gluconate, and after the administration of 100 grams of glucose and 45 units of crystalline zinc insulin in 350 ml. of distilled water. All tracings showed some degree of intraventricular block (QRS .13 second) and tall, pointed T waves, particularly noticeable in the precordial leads. There was little clinical change during or following these infusions. In contrast is the electrocardiogram following hemodialysis, which now showed no evidence of potassium intoxication. No changes appeared during the subsequent three days in spite of continued marked oliguria.

DISCUSSION

Disease states predisposing to elevation of the potassium concentration in extracellular fluid may progress to the point where the clinical syndrome becomes evident. In such cases the patient complains first of vague weakness, which may become manifest by obvious loss of muscular strength. This in turn progresses to complete flaccid paralysis of the extremities, accompanied by loss of tendon reflexes, and later to difficulty in phonation and respiration secondary to weakness of the musculature involved in these processes. *Preceding* this clinical picture and progressing pari passu with it are marked and characteristic electrocardiographic changes, the importance of which is evident when it is realized that the terminal event is cardiac asystole, often preceded by ventricular fibrillation or tachycardia. Frequently, even in severe cases, the patient is alert and apprehensive, even when muscular paralysis is apparent. Maintenance of consciousness and adequate levels of blood pressure until cardiac arrest is not infrequent.[35] Such was the picture in Case 8 of our own series. Cardiac irregularities or

bradycardia may accompany the clinical picture. The mental status is to some extent determined by the degree of azotemia and its concomitant drowsiness. It is not uncommon, however, in states of severe electrolyte imbalance, to see marked potassium intoxication in the face of minimal degrees of nitrogen retention. Addisonian crisis is an example.

A. Etiologic Factors Related to Potassium Intoxication: A number of factors partake in the production of potassium intoxication, and the presence of one or more of these should alert the clinician to the possibility. Of these, perhaps the most important is suppression of the urine volume. In our experience hyperkalemia, severe enough to be associated with the clinical syndrome, is a rarity in the absence of oliguria (less than 500 ml. per 24 hours). However, potassium intoxication may be observed in patients without oliguria or anuria in the presence of high potassium intake [2] or of sodium depletion, particularly when both occur simultaneously, as in Case 7, or when the rate of change in either direction is rapid.[7, 9, 36] Potassium clearance remains remarkably constant even in severe renal disease,[4] so that the limiting factor would seem to be the amount of urine secreted. In our patients with marked oliguria, the concentration of potassium in the urine often exceeded 60 milliequivalents per liter. In a urine volume of 100 to 200 ml. per day, however, this was inadequate to accommodate the demands for excretion of potassium supplied to the plasma by ingestion, catabolic processes, and shift from the cells. Other authors have stressed the necessity for oliguria or anuria in the production of hyperkalemia.[4, 9, 16] An increasing volume of evidence, including the cases reported here, attests to the probable importance of the syndrome of potassium intoxication as the cause of sudden, unexplained death in patients with anuria or oliguria. Stock [28] reports sudden death in three of his 22 patients with anuria, which in all probability was due to potassium intoxication. Immediately preceding death, the clinical condition of each patient was thought to be satisfactory. With recent evidence that temporary suppression of the urine may be compatible with life over a period of two to three weeks or longer, it is important that the recognition and treatment of this serious complication of urinary suppression be a matter of common knowledge.

The inability of the oliguric patient to excrete large quantities of potassium requires that his intake of potassium be negligible. If such a patient be maintained on parenteral fluids alone, this becomes a simple matter. However, the ingestion of food or fluids should be carefully supervised. Orange juice, one of the commonest of fluids administered to a hospitalized patient, contains relatively large amounts of potassium. A common source of exogenous potassium is the breakdown of red blood cells which occurs with an incompatible transfusion. Such a situation frequently is to blame for the subsequent anuria or oliguria, as well as for releasing potassium which the patient is then unable to excrete. Experimental work in animals has shown that intravascular hemolysis, by the rapid liberation of potassium,

may result in death.[20]   Any increase in the normal catabolic process results in increased tissue breakdown with the liberation of nonprotein nitrogen and potassium which cannot be removed from the extracellular fluid.   Fever, the post-surgical state, and any variant of the "alarm reaction" are examples of such processes and may increase the possibility of increased levels of extracellular potassium.

There is evidence that the abnormal metabolic status of the oliguric or anuric patient may predispose to transfers of potassium (without nitrogen) from its intracellular position to the extracellular fluid.   Such transfer has been found to occur in patients with renal insufficiency,[9] and under conditions of anoxia.[41]   "The expansion of extracellular volume in itself may lead to transfer of potassium from cells."[9]   Such expansion with resultant potassium transfer may occur as the result of the infusion of large amounts of hypertonic solutions at a rapid rate.   The infusion of hypertonic glucose solution may later result in hypotonicity as glucose is metabolized and excess water retained.   This latter effect of hypertonic glucose solutions decreases their long-term therapeutic value in potassium intoxication, although the immediate effect is salutary.

In our experience, severe degrees of acidosis predispose to potassium intoxication.   Correlation has been noted in both diabetic acidosis[24] and artificially induced acidosis[30] between low blood pH and the increased T waves seen in the electrocardiograms of potassium intoxication.   Hoffman has noted in nephrotics[6] that while red cell potassium could be increased by the administration of potassium chloride, this was not possible after the production of acidosis by ammonium chloride.   Martin and Wertman,[31] studying patients with severe diabetic acidosis, found that in spite of the acidosis a low serum potassium was correlated with low T waves, whereas Nadler,[24] in the same type of patient, found the height of the T wave and the serum potassium concentration to be correlated only when the latter was high.   It seems probable that acidosis per se is a factor in production of the potassium effect only as it affects potassium transfer or the ratio of the intracellular and extracellular ion.[7]

In alkalosis, on the other hand, it is usual to find a low level of extracellular potassium.[24, 54]   Such patients had adequate urine volumes or anuria of short duration.   One patient in our series with anuria of five days' duration and metabolic alkalosis had a serum potassium concentration of 8.5 mEq/L.   There were, however, no clinical or electrocardiographic signs of potassium intoxication.   Case 8, whose high normal serum carbon dioxide content represented a respiratory acidosis rather than metabolic alkalosis, illustrates the rapid progress of potassium intoxication in the acidotic patient.

B. *Diagnosis of Potassium Intoxication:* It must be emphasized that the chemical phenomenon of hyperkalemia may be completely unassociated with the clinical syndrome of potassium intoxication.   Earlier workers in the

experimental field [7, 37] felt that there was a very close correlation between the concentration of potassium in the serum and the electrocardiographic changes produced.   Subsequent experience,[12, 17, 39] however, has demonstrated that the correlation between the electrocardiographic changes and serum potassium level was crude, the appearance of the electrocardiogram at a given serum potassium level varying within a considerable range.   The present observations demonstrate further this lack of correlation.   Thus, in Case 2, the changes recorded when the serum potassium level was 9.5 mEq/L (figure 3B) were the most marked changes noted in this patient, yet a fall of only 0.4 mEq/L to 9.1 mEq/L (figure 4A) was accompanied by a most striking improvement in the appearance of the tall pointed T waves of the electrocardiogram, with a minor degree of auriculoventricular block being the only remaining change.   This disparity was emphasized when comparison was made between the serum potassium level and the electrocardiographic appearance in different individuals.   Thus a level of 8.8 mEq/L in Case 1 (figure 1) was associated with much more pronounced changes than were recorded in Case 2, with the higher level of 9.1 mEq/L (figure 4A).

Concurrent determination of the serum sodium level casts considerable light upon these inconsistencies.   In the cases in which these observations were made it was quite constantly observed that a normal serum sodium level antagonized the effect of hyperkalemia in producing its characteristic electrocardiographic effects.   Conversely, lowering the serum sodium level enhanced the effect of hyperkalemia (Case 4).   Figure 8 demonstrates graphically the effect on the electrocardiogram of similar serum potassium levels in the presence of varying sodium concentrations.   At the same time a necessary condition to the development of the characteristic electrocardiogram is some degree of elevation of the serum potassium level; a low serum sodium alone in the presence of a normal serum potassium is not capable of producing these changes in the electrocardiogram.

Although there is a lack of direct correlation between the absolute chemical values and the changes in the electrocardiogram, there is a parallelism between the electrocardiographic changes and the clinical state of potassium intoxication.   Since the concentration of other ions influences the toxicity of potassium, it is obvious that the serum potassium level itself is not necessarily a true index of the clinical state of the patient.   The electrocardiogram, however, records the totality of the effects of the ionic environment acting at the surface of the heart (and peripheral) muscle cell, and reflects faithfully the reaction of the cardiac muscle.   In this respect it is more useful than the determination of the serum concentration of the individual electrolytes and is the single most important guide to the progress and therapy of the patient with incipient or actual potassium intoxication. Our observations substantiate the conclusion that "The electrocardiogram is not properly a substitute for the measurement of the concentration of

serum potassium." [17]   It should be added, however, that the electrocardio-
gram is the more reliable clinical index and that the measurement of the
serum potassium is not properly a substitute for the electrocardiogram.

The sequence of changes occurring in the electrocardiogram with the
onset and progression of potassium intoxication are well documented.[7, 11, 12,]

TABLE I

Patient	Sex	Age	Diagnosis and Complications	Serum Na Values mEq/L		Serum K Values mEq/L		Result
				Initial	Final	Initial	Final	
1. J. C.	M	48	Subacute bacterial endocarditis and focal embolic glomerulo-nephritis. Oliguria and azotemia.	122 (134)	136 (—)	8.0 (8.8)	5.8 (5.5)	Died of K intoxication subsequent to complete renal failure.
2. J. B.	F	35	? Bilateral renal cortical necrosis following operative delivery for premature placental separation.	114	132	9.1	6.0	Recovered completely save for slight Raynaud-like Sx of both hands.
3. G. E.	M	68	Lower nephron syndrome due to intravascular hemolysis following transurethral resection of prostate.	127	127.5*	8.2	6.0*	Complete recovery.
4. K. B.	F	35	? Bilateral renal cortical necrosis following eclamptic delivery.	108	130	7.3	5.5	Complete recovery.
5. M. F.	F	35	? Bilateral renal cortical necrosis following eclamptic delivery.	100	122	7.0	5.5	Complete recovery.
6. V. F.	M	43	Acute dehydration following alcoholic psychosis. ? mild lower nephron syndrome.	136	—	8.5	6.0**	Not dialyzed. Complete recovery save for inability to concentrate urine.
7. D. O'L	M	65	Chronic glomerulo-nephritis and pyelonephritis; azotemia and urethral obstruction. Given K-loaded exchange resin.	112	134†	11.5	9.0†	Not dialyzed. Recovered with glucose, bicarbonate and insulin i.v.
8. G. W.	M	25	Lower nephron syndrome following massive transfusion for blood loss during resection and graft for coarctation of aorta.	129††	—	8.5††	—	Died of K intoxication 3rd p.o. day. Not dialyzed.
9. J. L.	M	16	Lower nephron syndrome following massive transfusion of both bank blood and autotransfusion during resection of coarctation of aorta.	130	140	8.5	7.0	Sudden death eleventh p.o. day (?) due to rupture of suture line in aorta.

Unless otherwise stated the initial and final values represent the pre- and post-dialysis
sodium and potassium concentrations in serum.   Patients 6, 7 and 8 were not dialyzed.
  * Serum levels after 3 hours of dialysis.
  ** Serum potassium level 3 days after initial values. EKG normal at this time.
  † Serum values 2 hours later during which time patient had been treated with glucose-
insulin-bicarbonate mixture.
  †† Serum values taken 5 hours before death.

[15, 16, 37, 38]   This sequence is characteristic and constant, a fact which en-
hances the value of the electrocardiogram as a diagnostic tool.   The changes
described and seen in our series have been summarized in table 2.   They
consist of: (1) the development of tall, narrow, pointed T waves; (2) de-
pression of the S–T segment which tends to become a direct line from the
nadir of the S to the apex of the T wave; (3) auriculoventricular block;

TABLE II

Schema showing the electrocardiographic manifestations of hyperkalemia. Note that tall pointed T waves and prolongation of electrical systole are the earliest changes recorded. There is considerable overlap in time sequence of subsequent changes. Lest the table be misleading and for the sake of completeness, the more advanced changes are shown in the right side of the chart; these are more fully considered elsewhere.[55]

SCHEMATIC DIAGRAM OF SEQUENTIAL CHANGES IN ELECTROCARDIOGRAM IN POTASSIUM INTOXICATION

I. DIFFERENTIAL CHANGES IN VENTRICULAR ACTIVATION → TALL POINTED T WAVES, PROLONGED Q-T INTERVAL → DECREASED R WAVES, INCREASED S WAVES, DEPRESSED R-ST SEGMENTS

II. INTRA-AURICULAR BLOCK → PROLONGED P WAVES, LOW P WAVES → AURICULAR STANDSTILL, AURICULAR FIBRILLATION → IDIO-VENTRICULAR RHYTHM

III. AURICULO-VENTRICULAR BLOCK → PROLONGED P-R INTERVAL --> HIGHER GRADES OF A-V BLOCK (UNIMPROVED)

IV. INTRAVENTRICULAR BLOCK → PROLONGED QRS INTERVAL → DIFFUSE INTRAVENTRICULAR BLOCK, BUNDLE BRANCH BLOCK → VENTRICULAR STANDSTILL

V. ECTOPIC RHYTHMS → VENTRICULAR ESCAPE BEATS, PREMATURE " → VENTRICULAR "FLUTTER" AND TACHYCARDIA → VENTRICULAR FIBRILLATION

(4) decreased amplitude and increased duration of the P waves, and eventually auricular standstill; (5) intraventricular block of progressively increasing grade associated with a decreased height of the R waves and an increased depth of the S waves; (6) prolongation of the Q–T interval; (7) a ventricular arrhythmia variously regarded as due to auricular fibrillation or sinus arrhythmia and occasionally due to ventricular ectopic beats; (8) sinus bradycardia; (9) disintegration of the ventricular complexes culminating in a baseline having the appearance of a continuous sine wave, and (10) ventricular standstill. Although there is some overlap in their time relationships, a certain degree of intraventricular block, for example, developing simultaneously with auriculoventricular block, this is the general sequence of the changes noted.

Finch et al.[12] have demonstrated that the electrocardiographic changes of potassium intoxication are much more clearly exhibited in certain of the bipolar chest leads (CF leads) than in the conventional limb leads. The present studies confirm this observation with regard to unipolar chest leads taken in the manner of Wilson. However, very slight changes in the position of the chest electrode with relation to the heart may produce profound changes in the potential of the various electrocardiographic deflections recorded over the precordium, and it is exceedingly difficult to take precordial leads in precisely the same point at successive times. For the purpose of following such changes then, it is useful to have marked on the patient's chest the position of the electrodes so as to duplicate the anatomical relationships as nearly as possible. On the other hand, because of the fixed insertion of the extremities with relation to the trunk, such variations are not encountered in the use of limb leads. Hence, once the electrocardiographic diagnosis of potassium poisoning has been made, the changes in the precordial leads may be correlated with those in one of the limb leads and the patient's electrocardiogram can be followed along merely by making continuous recordings of one of the limb leads (e.g., figures 3C and 1E).

The value of the electrocardiogram as the first clue to the existence of potassium poisoning was convincingly demonstrated in the present study. This emphasizes the importance of frequent electrocardiographic examination to detect early evidence of potassium poisoning in anuria, from whatever cause. The earliest electrocardiographic sign recorded was the presence of tall, pointed T waves. Peaking of the T wave may not be a striking change. Unless one is alert to the possibility of potassium intoxication, this alteration may pass unnoticed. Even when aware of the possibility it may be impossible to be sure of just what is a normal and what an abnormal pointed T wave in any individual electrocardiogram. The situation may be clarified by serial tracings in which the evolution of the T wave changes may be observed. The importance of such comparison with other tracings cannot be overemphasized and it is illustrated graphically by Case 8, in which the electrocardiogram taken the morning of death appeared to be

within normal limits.   Only when it was compared in retrospect with the previous tracing did the diagnosis become obvious.

It is significant that in Case 8, and in another of our cases not here reported (P. B. B. H. No. 8A877), the inverted T waves of left ventricular hypertrophy become upright and tall in the presence of potassium intoxication.   This change has been reported by others.[40]

C. Treatment of Potassium Intoxication: An evaluation of the *methods of treatment* available is of the utmost importance, since rapidly fatal potassium intoxication may occur in totally reversible acute renal insufficiency. One of the purposes of this study was the evaluation of these methods.

Calcium Therapy: It has been appreciated since the classic observations of Sidney Ringer [1] that calcium salts combat the toxic effect of potassium upon the heart of the experimental animal.   This fact has been noted in more recent years by Winkler et al.[20]   Recently this chemical antagonism has also been reported in states of hypocalcemia.[42]   In Finch's cases [12] it was found that calcium increased the frequency of ventricular contractions but was less effective in overall therapy than was the infusion of sodium. This is in accord with the conclusions of Tarail.[17]   In our series, calcium in the amounts administered had little effect with the exception of Case 5, in which the change in serum calcium level may have played a rôle.

Sodium Therapy: The physiologic antagonism of sodium and potassium is well known,[18, 19] and infusions of hypertonic saline have been suggested in the therapy of hyperkalemia by Finch et al.[12]   These authors stressed the rôle of low serum sodium in aggravation of the clinical status and reported marked improvement with the infusion of hypertonic sodium chloride.   It is possible that this may be correlated with the observation that acidosis enhances the possibility of potassium intoxication, both mechanisms stemming from an intracellular movement of the sodium ion.[25]   A similar disappearance of sodium from the extracellular fluid without exogenous loss has been reported in nephrectomized dogs by Vanatta [39] and has been a frequent finding in our anuric patients.   Other observers have found saline infusions to be of little benefit.   Elkinton [9] found the use of hypertonic saline in one case ineffectual.   Tarail [17] in one case (P. M.) noted that following the infusion of 500 ml. of 3 per cent sodium chloride the serum potassium actually rose from 7.2 to 8.3 milliequivalents per liter.   In one of Finch's cases [12] the infusion of a total of 15.3 grams of sodium chloride resulted in a rise in serum potassium from 9.7 to 9.8, although the electrocardiogram improved.   In another instance 370 ml. of 3 per cent sodium chloride caused a remission of symptoms for only 40 minutes.   The brief duration of the effect of hypertonic saline has been noted also in our cases (Cases 3 and 4). There is some evidence that hypertonicity of the extracellular fluid may be a stimulus for the intracellular movement of sodium.[32]   If this is so, the infusion of hypertonic sodium solutions may ameliorate the effect of hyperkalemia temporarily, but when equilibrium is reached with the intracellular

compartment, particularly if it occurs at the expense of intracellular potassium causing its migration into the extracellular fluid, the net result will be one of aggravation. In any case, the infusion of large amounts of sodium and water into a patient who is unable to excrete them poses the problem of expansion of extracellular volume and pulmonary edema. Our experience indicates that the infusion of sodium may be of marked benefit where specific sodium depletion has played a rôle in the production of potassium intoxication (Case 7). We have found that it is a more valuable agent than calcium but that its effect is temporary, and that in the patient whose hyponatremia is due to intracellular movement of sodium rather than exogenous loss it is of little real benefit in correcting low serum sodium values or acidosis.

Glucose and Insulin: Decrease in extracellular potassium levels following the administration of glucose and insulin has been recognized for some time,[21] and hypokalemia is a not infrequent sequel to the treatment of diabetic coma with large doses of insulin.[22, 23, 24] Moore and Stewart [43] noted the disappearance of one of the electrocardiographic signs of potassium intoxication following the intravenous injection of hypertonic glucose solution. Bywaters [13] was one of the first to suggest the use of this method to combat clinical hyperkalemia. It appears that the mechanism by which reduction of potassium occurs is the formation of a monopotassium salt and its deposition with hexosediphosphate during the process of glycogen formation and storage. Later in the process the potassium and phosphate are released from combination and made available for excretion.[21, 34] This would account for the immediate improvement in glucose-insulin treatment of potassium intoxication, and the later regression of symptoms and signs. Our feeling is that glucose and insulin infusion is the most valuable and least hazardous of the parenteral forms of therapy. Its effect appears to be of greater duration and most consistently reproducible. Its effect can be seen following maximum sodium and calcium effect (Cases 3 and 4) and, conversely, it is true that in some cases further sodium therapy produced no effect after infusion of glucose and insulin.

Hormonal Therapy: The retention of nitrogen, phosphate and potassium has been demonstrated to follow the administration of testosterone, particularly as the propionate.[47, 48, 49] This is presumed to be secondary to retention of these substances within the cell, where they are thus made unavailable to the extracellular fluid. This "anabolic effect" of testosterone may be of importance in preventing to some extent rapid release of phosphate, nitrogen, and potassium to the extracellular fluid of the anuric patient. On this basis it has been our custom to administer testosterone propionate, in an initial dose of 50 mg. intramuscularly, to be followed by 25 mg. daily for four to five days. A theoretical objection to this has been raised by the statement of Thompson,[50] who found that testosterone propionate in doses of 50 mg. daily caused a rise in the basal metabolism of "as much as 35 to 40 per cent

above normal." On the other hand, Kinsell et al.[51] found in one male patient receiving 150 mg. of testosterone propionate daily that the basal metabolic rate was not significantly changed. This lack of change in basal metabolic rate was also noted by Kenyon.[49] The apparent increase in kidney mass and tubular hypertrophy found after the administration of testosterone [47] may have some application to the healing of the renal lesion in the patients with "lower nephron nephrosis."

The adrenal steroids, either exogenous or produced by the administration of adrenocorticotropic hormone, may be of some benefit in the prophylaxis of potassium intoxication. There is suggestive evidence [52] that under their influence a decrease in serum potassium is facilitated, presumably by intracellular shift, during the administration of glucose and insulin. It has also been shown in animals that the administration of adrenal cortical extract protects against the toxic effects of potassium administration.[53] A theoretical objection to this therapy in the anuric patient is the known effect of the adrenal hormone in increasing the accumulation of nitrogen (in the face of inadequate renal function).*

Artificial Methods of Removing Potassium: The extrarenal removal of potassium from the extracellular fluid has been suggested [9] and evidence published that this may be effectively accomplished by the artificial kidney in animals [26, 27] and in the human.[33, 44, 45] The removal of potassium in a case of clinical intoxication has also been reported by means of perfusion of the large bowel.[46] Since the perfusing fluid contained saline and hypertonic glucose, however, it is not clear how much of the beneficial effect was due to removal of potassium ion and how much to the absorption of sodium chloride and glucose. Of the methods available, however, there is no question from our data but that dialysis, which permits artificial removal of potassium and simultaneous correction of acidosis is the most effective and lasting method, its effect being complete and measured in terms of days, as opposed to the infusion of glucose and insulin in the amounts used, where the effect is often partial and measured in terms of hours. Dialysis has also been shown to effect marked changes following maximum benefit from the other forms of therapy.

Cation exchange resins represent an effective method of removal of potassium, but at the present time their use is limited in situations such as those presented here. These resins require a certain period for their activity to be felt, since they must pass through the alimentary canal to a point where the potassium will be available to them. They must be given in fairly bulky quantities and their action is not entirely predictable nor quantitative.

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* Since submission of this manuscript we have noted the failure of large amounts of desoxycorticosterone acetate (DOCA) to prevent or arrest the development of severe potassium intoxication in a patient with lower nephron nephrosis. It is our feeling that if further clinical trial is given the adrenal steroids in hyperkalemia of anuria, it should be with cortisone or whole extract and that therapeutic measures of proved efficacy should be readily available.

COMMENT

An opportunity to evaluate the available forms of therapy has been afforded in the present series, in some cases the effects of the various methods being observed in sequence in the same patient during a prolonged state of intoxication. These observations have been recorded in the protocols. Thus, in Case 1, the calcium solution produced very little and the glucose solution no effect. By exclusion it was apparently either the insulin in the calcium-glucose-insulin mixture or the combination itself which had produced the most striking electrocardiographic effect. It is possible, if the order of injections had been changed and the glucose given first, that glucose rather than calcium might conceivably have produced slight shortening of the QRS interval. The decisive observation of the effect of insulin alone was not made in this patient. But from these observations and other evidence [21] indicating that insulin acting upon endogenous or exogenous glucose as a substrate is capable of producing these changes, the inference seems warranted that the changes would have been produced by insulin alone or insulin plus glucose. The chemical data in Case 1 are inconclusive but suggest that insulin-glucose is superior to calcium or to glucose alone in combating hyperkalemia. The significant improvement which occurred in Case 5 after 3 grams of calcium chloride were given intravenously stands in contrast to the findings in Case 3, where 4 grams of calcium gluconate had no effect on the electrocardiogram. Unfortunately, serum calcium levels were not obtained in the latter case. In Case 5 the serum calcium was elevated from 3.4 to 5.9 milliequivalents per liter after intravenous calcium therapy, and this may have some bearing on the improvement, although in Case 9 (figure 11) a rise in serum calcium of 4.0 to 6.8 mEq/L had little effect on the electrocardiogram. The beneficial effects of glucose and insulin on the clinical state and the electrocardiogram were constant in all cases. That the effect was transient, however, is well demonstrated by the rate of reversion in Case 5, where the electrocardiogram had reverted to pre-infusion levels (figure 7C) four hours after the end of the infusion. This fact may perhaps be explained by the release of potassium from the hexosediphosphate combination as noted above.

The conclusion that the effect of sodium infusion, either as the chloride or the bicarbonate salt, is inferior to glucose-insulin is supported by our observations. The transient beneficial effect is well seen in Cases 3 and 4, where the improvement was of less than 20 minutes' duration and was followed, if anything, by an aggravation of the clinical state. It is likely also in Case 2 that the amount of sodium chloride required to produce the changes brought about by relatively innocuous amounts of glucose and insulin would have been enough, in this anuric patient, to produce dangerous augmentation of the extracellular fluid volume. Thus in the present investigation the combination of glucose and insulin was, next to hemodialysis, the most effective form of therapy in combating the electrocardiographic and clinical

manifestations of hyperkalemia.   In general, glucose-insulin was capable of further amelioration of the electrocardiographic abnormality when the maximal effect of sodium or calcium or both had already been obtained. The formula for composition of this infusion was roughly one unit of regular insulin per two grams of glucose, the latter being made up in a 20 to 25 per cent solution, and given in a volume commensurate with what it was felt the anuric patient could safely tolerate.

Yet even this effect was partial at best and transitory in its benefits, evidence of intoxication returning within hours.   In all cases in which these chemical measures preceded the use of hemodialysis, the latter effected more complete changes with a return to a normal electrocardiogram or to what was the usual electrocardiogram for the patient being treated.   In addition, relative to the duration of improvement brought about by the chemical procedures, the changes following hemodialysis were either permanent (if diuresis supervened) or persisted over several days in spite of continued anuria.   The superiority of this method of treatment lies in the facts that potassium ion is being removed from the blood (in Case 2, 4.7 gm. of potassium were recovered from the dialyzing fluid), acidosis is corrected by the removal of acid metabolites, and sodium is supplied to the extracellular fluid without the addition of water, this latter effect being accomplished without increasing tonicity as retained metabolites are removed concurrently.

SUMMARY AND CONCLUSIONS

1. Hyperkalemia may be a fatal accompaniment of oliguria or anuria associated with potentially reversible renal damage.

2. Characteristic changes in the electrocardiogram represent the earliest detectable sign heralding the onset of the clinical syndrome of acute potassium intoxication.   Frequent electrocardiographic examination is indicated in all patients with anuria or oliguria.

3. Clinical and electrocardiographic evidence of potassium intoxication cannot be correlated with the absolute concentration of potassium in the blood.   An important factor is the concomitant serum sodium concentration. A low serum sodium augments changes produced by any given increase in serum potassium.

4. The abnormal electrocardiogram reflects the composite effect of several chemical changes.   As such, it is a more reliable guide to the overall clinical status than the determination of any one chemical change in the blood.

5. Glucose and insulin administration is the most effective immediate chemotherapeutic approach to the treatment of potassium intoxication.   Its effect is more pronounced and lasting than that obtained by the administration of either sodium or calcium salts.

6. Hemodialysis produces more profound and persistent effects than any of the parenteral forms of treatment enumerated.   This effect is achieved by the combined effects during dialysis of the addition of glucose, the re-

moval of excess potassium, the addition of sodium, the correction of acidosis, and the removal of toxic metabolites.

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BIOCHEMICAL STUDIES IN MULTIPLE SCLEROSIS *

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THE consideration of multiple sclerosis as a metabolic disease is not new. The literature, both European and American, throws little light, however, on the chemical changes in this syndrome. Jelliffe[1] in 1921 stated the possibility that the neurologic lesions were of metabolic origin. German investigators[2,3] reported elevated serum cholesterol values. In this country Brickner[4] found abnormal lipolytic activity in the blood. Crandall and Cherry[5] noted the similarity between the lipase activity in multiple sclerosis and in liver diseases. Weil and Cleveland[6] likewise found abnormal serum lipase but did not consider it peculiar to the disease, since similar results were found in other pathological states. Weil[6] further reported low serum inorganic phosphorus. In 1948 Weil and Bradburne[7] reported that patients with multiple sclerosis were in phosphorus balance on an intake of about 700 mg. phosphorus per day, as compared with 2000 mg. required for normal subjects. He relates this finding to disturbed phospholipid metabolism. Goodall and Slater[8,9] treated multiple sclerosis as a deficiency disease, using diets containing one-half pound of liver per day, and later supplementing this diet with other vitamin-rich foods. The use of vitamins in therapy was reported on by Moore[10] in 1940, and he discussed the action of the vitamins administered on carbohydrate metabolism.

Preliminary studies in our laboratory showed that individuals with multiple sclerosis had elevated blood pyruvic acid values in the fasting state. This finding, combined with the clinical observation that the patients had increased symptomatology with high carbohydrate intake, focused our interest on carbohydrate metabolism. Under glucose stress the biochemical pattern was found to be distinctive and to give considerable information on the nature of the syndrome. We believe the biochemical evaluation to be equally as important as the neurologic examination.

MATERIAL

The cases were studied as they appeared for medical care. The diagnosis was established by two or more examiners, working independently. No exclusions or inclusions were made because of severity or duration of symptoms. Fifty cases have been studied during the two-year period of this investiga-

tion.   Blood and urinary excretion changes after the oral ingestion of glucose were recorded on the 50 cases and on 30 healthy controls.   Controls were selected from varying occupations, age groups and morphologic groups to match those of the patients.   Urine studies were started later in the project than the blood studies, so excretion data are available on only 28 cases and 20 control subjects.

METHODS

With the individual under basal conditions in a quiet room of constant temperature and humidity, 1.25 gm. of glucose per kilo of body weight were administered orally.   This relatively small amount of glucose was used because it gave essentially the same peak as larger amounts but the time required to elicit the different phases of the curve was shortened.   The diet of the individual prior to the test was standardized by having him on a "general" hospital diet, or its equivalent, at least three days before the studies were made.

Zero and hourly blood samples were obtained for four hours.   Special precautions were taken in drawing the blood to avoid stasis by tourniquet and to avoid hemolysis.[11]   A cold tube containing 5 mg. of sodium fluoride,[12] 15 mg. of iodoacetic acid, and 12 mg. of potassium oxalate was used to receive 3 ml. of blood, immediately after collection, for use in the analysis of sugar, lactic acid and pyruvic acid.   The tube and its contents were kept ice cold until analyzed.   It was found that blood could be thus kept for 24 hours if necessary.   The analytic procedures were modified so that complete analysis could be done with 25 ml. of blood for the zero sample and 15 ml. for each successive sample.   Each blood sample was analyzed for glucose,[13] lactic acid,[14] pyruvic acid,[15] and the zero sample for hemoglobin[16] as well as the above components.   Serum from each sample of blood was studied for potassium,[17a, b] sodium,[18] calcium,[19] inorganic phosphorus,[20] magnesium,[21] proteins,[22] and true and total cholinesterase.[23]   In addition, the following were determined on the zero sample: cephalin flocculation,[24a, b] cholesterol and cholesterol esters,[25] bilirubin,[26] and alkaline phosphatase.[27]   When about half of the studies had been made, it became evident that serum sodium, calcium, proteins, and total cholinesterase values were not changing significantly during a test, so they were thereafter determined on the fasting sample only.   Magnesium determinations were discontinued, for there was no apparent difference between the normal and pathologic groups.   True cholinesterase in serum was discontinued, for there was no pattern in its fluctuation during a single test on an individual and no interpretation could be made from case to case.   Prothrombin time was determined on 17 unselected patients by the Quick technic, using diluted plasma.[28a, b]   A control was run parallel with each patient and the technic carried out by one technician in a single laboratory.

The overnight urine sample was discarded and the zero sample taken as that sample voided (or collected by catheter) during the one to two hours

just before administration of glucose.   A urine sample was collected each hour for four hours after the glucose was given.   Urine volumes were measured and each sample analyzed for total nitrogen,[29] uric acid,[30] creatine and creatinine,[31] sodium,[32] potassium,[17a, b] chloride,[33] inorganic phosphorus,[20] and qualitatively for reducing sugar and protein.

RESULTS

The data presented here have been subjected to statistical analysis.   The details of analysis are not included but the word "significant" has been used with the mathematical meaning.

BLOOD STUDIES

Figure 1 shows graphically the average values for glucose, lactic acid and pyruvic acid.   The bottom curve is the ratio of pyruvic acid to lactic acid.   The average zero pyruvic acid values for the controls, the group in remission and the group in relapse are 1.22, 1.31, and 1.77 mg./100 ml., respectively.   As is shown in the figure, the most striking difference in the three groups is the elevated mean pyruvic acid values in those in relapse.
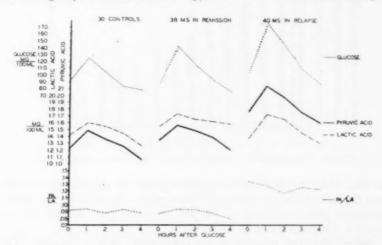
FIG. 1.   Effect of oral glucose on blood glucose, pyruvic acid, lactic acid and PA/LA.

The difference between the values in this group and in the controls is highly significant throughout the test.   Pyruvic acid increases to a higher level after glucose in those in remission than in the controls, and significantly so in the second, third, and fourth hours.

The mean values for lactic acid are not significantly different in the three groups, but are shown along with the glucose and pyruvic acid values to

illustrate that in these two closely related metabolites of glucose it is pyruvic acid that is most dislocated.

To reduce the pyruvic acid and lactic acid values to a single value so as to simplify interpretation of results, the ratio of pyruvic acid to lactic acid was calculated.   We have found it a convenient figure.   If the ratio is above 0.1 it indicates the accumulation of pyruvic acid out of proportion to lactic acid and has been found consistently in the individuals in relapse.   The ratios at the zero hour were 0.088, 0.086, and 0.130 for the controls, the group in remission and the group in relapse, respectively.   Throughout the tolerance test the ratios in the group in relapse are significantly elevated above the controls.

That the tolerance for glucose is lower in the group of patients in relapse is evident.   Glucose in the active group is significantly elevated throughout
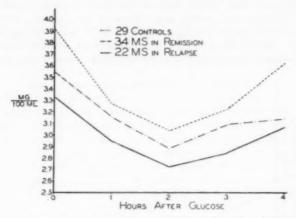
Fig. 2. Serum inorganic phosphorus during oral glucose tolerance test.

the test, while the values in the quiescent group are significantly different from the controls the first and second hours only.   Due to the many factors influencing glucose tolerance, as diet and physical activity, caution was observed in interpreting glucose levels.

Serum inorganic phosphorus was consistently found to be low.   The results are shown in figure 2.   The zero value in the patients in relapse averages 3.28 mg./100 ml., as compared to 3.57 in those in remission and 3.92 in the controls.   The values in the group in relapse are significantly lower than the controls at the zero, second, third, and fourth hours.   The mean values for those in remission are lower than the controls, but the difference is significant for only the zero and fourth hours.

Of the other electrolytes, potassium was of interest in individual cases

but no constant or characteristic abnormality was found.   The same could be said of serum calcium and sodium.

Serum proteins were lower in the multiple sclerosis groups but not significantly so.   Total cholinesterase was of interest in following individual cases, for the fall in activity seemed to precede exacerbations.   However, since the average of the cholinesterase values or a single cholinesterase value in a patient was not significant, these will not be discussed in greater detail. Hangar cephalin flocculation was positive in 50 per cent of the cases.   This is not different from the findings in a miscellaneous group of chronically ill patients with other diseases.   Blood hemoglobin values were not significantly different in the multiple sclerosis patients.   In some individuals, low values were common but were not frequent enough to be characteristic of
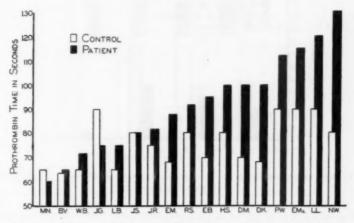
Fig. 3. Quick's prothrombin time (diluted plasma) of 17 unselected multiple sclerosis patients.

the disease.   Serum bilirubin and alkaline phosphatase were within normal limits in every case.
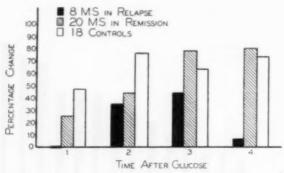
Prothrombin time was determined in 17 unselected cases.   Fifteen of the 17 were prolonged.   Figure 3 shows the results.   The two cases not prolonged were static and of long duration.   However, the degree of prolongation did not parallel the clinical condition.

Serum total cholesterol was significantly elevated in the patients.   The following mean values, ± standard error, were found: 25 patients in relapse, 271.1 ± 6.7; 38 patients in remission, 266.5 ± 7.14; 30 controls, 230.0 ± 7.41.   High total cholesterol was a constant finding.   In individual cases a fall in cholesterol generally paralleled clinical improvement.   The cholesterol esters were also increased so that the per cent of total cholesterol esterified ranged between 65 and 80 with no exceptions.

URINARY STUDIES

In each urine sample, total nitrogen, uric acid, sodium, potassium, chloride and inorganic phosphorus were each calculated in ratio with preformed creatinine. This means of expressing the data was as used by Thorn.[34] For each substance the percentage change from the zero sample of each of the four hourly samples was calculated. Of the above named products, noteworthy differences between the patients and the controls were found in uric acid and inorganic phosphorus. Urine studies were made on 28 multiple sclerosis patients and 20 controls. Additional data are needed before conclusions can be drawn on the suggestive differences in some of the other substances.

FIG. 4. Mean percentage change from zero sample in urinary excretion of $\frac{uric\ acid}{creatinine}$ during oral glucose tolerance test.

Figure 4 gives the results of the percentage changes in uric acid/creatinine excretion following the ingestion of glucose in eight multiple sclerosis patients in relapse, 20 in remission, and 18 controls. The patients in relapse showed less change in the excretion of uric acid after glucose. The average changes during the test for this group were 0, + 34, + 43, and + 3 for the four hours of the test, as compared to + 46, + 76, + 62, and + 73 for the controls. The group in remission had a greater increase in uric acid than the control subjects the third and fourth hours, the actual changes being + 24, + 43, + 79, and + 80 per cent. Because of the small number of cases studied these differences are not significant, but the low uric acid excretion the first and fourth hours in those in relapse was a consistent finding in the eight cases.

Figure 5 shows the percentage change from the zero sample in the excretion of inorganic phosphorus/creatinine during the glucose tolerance test in 25 multiple sclerosis patients and 19 control subjects. The pathologic group was not divided into subgroups, for there was no apparent relation-

ship between phosphorus excretion and activity of the disease. In the patients the excretion of inorganic phosphorus/creatinine was increased over the zero sample by 21, 72, 24, and 25 per cent for the four successive hourly periods. In the controls there was 30 per cent increase the first hour but a decrease, compared to the zero sample, of 33, 41, and 36 per cent for the
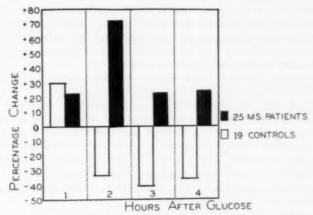
FIG. 5. Mean percentage change from zero sample in urinary excretion of $\frac{\text{inorganic phosphorus}}{\text{creatinine}}$ during oral glucose tolerance test.

second, third, and fourth hour periods. The findings show that in the pathologic group, glucose results in a relative loss of phosphorus from the body, while in the controls the ion is conserved after the first hour.

In none of the individuals was an appreciable amount of creatine, glucose or protein excreted.

DISCUSSION

It is now an accepted fact that the metabolism of carbohydrates results in the formation of pyruvic acid. The further oxidation of this intermediate metabolite requires oxygen and cocarboxylase. Lactate is produced by the reduction of pyruvate. Bueding et al.[35] demonstrated that blood pyruvate was elevated following the ingestion of glucose in normal individuals. In conditions associated with thiamine deficiency they[35] found that the fasting blood pyruvic acid was elevated, and the pyruvate curve after glucose ingestion was abnormally elevated and prolonged. Goldsmith[36] found that the administration of glucose resulted in an increase in both pyruvic and lactic acids, and that the lactate/pyruvate ratio was essentially the same as in the basal state. Goldsmith[36] further reported that exercise produced a greater increase in lactic than in pyruvic acid. Friedemann et al.[37] reported that

lactic acid was increased in anoxia in normal individuals to a greater extent than pyruvic acid. In tests carried out on diabetic subjects, Klein[33] found variations in blood pyruvate accompanied by simultaneous and similar changes in blood lactate.

From our studies it is evident that in multiple sclerosis there is an abnormal metabolic pattern in the metabolism of carbohydrate, in which there is a partial block at the pyruvic acid level. In the limited number of closely related demyelinating diseases studied we have not found a similar pattern. The persistence of low serum inorganic phosphate and increased excretion of this ion after glucose may be a reflection of an abnormality of energy transfer which becomes manifest after puberty.

The finding of elevated serum cholesterol in multiple sclerosis is in agreement with the reports by Frisch[2] and Pichler and Reisner.[3]

Without additional investigation to give information regarding the enzyme and endocrine systems involved, one could only theorize on the interrelationship of the abnormal findings reported. However, high blood pyruvic acid/lactic acid, low serum inorganic phosphorus with increased excretion of phosphorus after glucose, and elevated serum cholesterol have proved helpful in establishing diagnosis. The findings reported here indicate a general metabolic disorder rather than an anatomic change solely in the central nervous system.

SUMMARY

In multiple sclerosis there is an abnormal response to oral glucose, the most striking evidence of which is an elevation of pyruvic acid out of proportion to lactic acid. In those in relapse, the fasting level of pyruvic acid is high and remains so throughout the four hours of the test. In those in a less active stage of the disease, the disproportion of pyruvic acid to lactic acid is not shown until the second, third, and fourth hours after glucose. Serum cholesterol is elevated and is higher in the active case than in the quiescent one. Serum inorganic phosphorus is significantly lower. The excretion of inorganic phosphorus, expressed in ratio with preformed creatinine, is increased in the multiple sclerosis patients over the zero sample by 72, 24, and 25 per cent the second, third, and fourth hours after glucose, as compared to a decrease of 33, 41, and 36 per cent during the corresponding periods in the controls. The excretion of uric acid/creatinine after glucose is lower than normal in the individuals in relapse, being little changed from the zero sample in the first and fourth hours.

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EFFECTS OF NITROGEN MUSTARD ON THE BONE MARROW IN POLYCYTHEMIA VERA *

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SINCE there is as yet no knowledge of the cause of the increased rate of erythrocyte production in polycythemia vera, the most desirable therapeutic agent for this disease, from a theoretical standpoint, is one which can be given in dosage sufficient to depress the abnormal rate of mitosis in the erythropoietic tissue without seriously affecting the bone marrow cells which give rise to the granulocytes and platelets. At present, it is believed that the agent which most nearly fulfills these criteria is irradiation, by means either of roentgen-rays or of radioactive phosphorus. Recently, however, nitrogen mustard has received attention as a potential therapeutic agent for polycythemia vera,[1, 2] because of the apparent similarity of its mode of action to that of irradiation and the similarity of the qualitative clinical response obtained by the use of the two agents. The faculty possessed by nitrogen mustard of exerting its action to a greater extent on tissue cells having the highest rate of mitosis and to a lesser extent on those with a lower, or normal, rate of mitosis makes its use a rational approach to the treatment of such a condition as polycythemia vera. In order to determine its value, it is important to observe the effects wrought by this agent on the bone marrows of patients suffering from this disease.

It appears likely that the hematologic effects noted after nitrogen mustard therapy are the results of several different types of action by this agent on hematopoietic cells, namely, inhibition of mitosis, direct nucleotoxic action, toxic cytoplasmic changes, and actual cell destruction. Experimental work has indicated that the effects exerted on various types of cells by the mustards vary with the dosage of the agent employed. Relatively small doses may result in inhibition of mitosis without visible evidence of nuclear or cytoplasmic injury, while somewhat larger doses may cause the appearance of nuclear fragmentation; such fragmentation and abnormal chromatin dispersal were considered to be evidences of pathologic and incomplete mitosis.[3] Definite cytoplasmic changes were also found to occur after exposure to dilute solutions of the mustards.[4] Increased hemolysis of erythrocytes after nitrogen mustard therapy is indicated by increased excretion of urobilinogen, and the reticulocyte percentage in the blood declines concomitantly with the reduction of erythrocyte precursors in the bone marrow during the first week after the institution of treatment.[2] Jacobson and co-workers[2] stated that the reduction of hemoglobin and erythrocytes resulting from nitrogen

mustard therapy in patients with polycythemia rubra was greater than that noted in patients receiving this treatment for other diseases.

It is the primary purpose of this paper to present data bearing on the findings in the bone marrows of patients with polycythemia vera who were treated with nitrogen mustard. A secondary aim is to set forth some general observations on the cellular composition of the bone marrow in polycythemia vera. The main objectives in this study were to attempt to determine whether there is indeed any indication that there is a greater degree of action of this drug on the tissue believed to have the greatest mitotic activity in polycythemia vera—the erythropoietic tissue—than on other hematopoietic cells, and to try to settle on a rational plan of treatment utilizing the properties of nitrogen mustard to the greatest advantage.

PROGRAM OF TREATMENT AND INVESTIGATION

During the past 18 months, 11 patients with polycythemia vera have been treated with nitrogen mustard in the Mayo Clinic. In each case the diagnosis was established on the basis of the clinical picture, the presence of characteristically elevated values for hemoglobin and circulating erythrocytes, increase of the volume of packed erythrocytes, increase of the total blood volume, and the absence of any of the lesions to which polycythemia may be secondary. Specimens of bone marrow were obtained by sternal aspiration both before and at varying intervals after institution of nitrogen mustard therapy in six of these patients, and in two others specimens were obtained before treatment only. The pretreatment blood findings and the bone marrow findings before and after treatment in these eight patients furnished the data presented in table 1.

In treating these patients and obtaining the bone marrow specimens, the following program was carried out in each case. When the diagnosis of polycythemia vera had been established, phlebotomy was performed sufficiently often to reduce the volume of packed erythrocytes to approximately 50 to 60 c.c. per 100 c.c. of blood. Sternal aspiration was then done immediately prior to institution of nitrogen mustard therapy. Nitrogen mustard (methyl-bis [β-chloroethyl] amine hydrochloride) was then given intravenously in a total dosage of 0.4 mg. per kilogram of body weight, either as two injections of 0.2 mg. per kilogram each or as four injections of 0.1 mg. per kilogram each, on successive days. Sternal aspiration was performed in cases 1 through 6 at varying intervals after the initial injection of nitrogen mustard, as indicated in table 1. A general survey of the number and types of cells composing the marrow in each case was made from the small bits of marrow tissue aspirated, smeared directly on slides and stained by the Wright technic. The differential counts of marrow cells which furnished the figures shown in table 1 were made on smears prepared, by Schleicher's method,[5] from the "myeloid-erythroid layer" of cells which separates as a result of the centrifugation of the fluid portion of the bone marrow material.

TABLE I

Changes in Cellular Composition of Bone Marrow in Polycythemia Vera after Nitrogen Mustard Therapy

Case, Sex, Age, yrs.	Interval after Beginning Treatment*	Blood			Bone Marrow†									Period Followed and Clinical Course after Treatment
		Leukocytes, thousands per cu. mm.	Erythrocytes, millions per cu. mm.	Vol. Packed RBC, c.c. per 100 c.c. Blood	Erythroid Series				Myeloid Series				Myeloid: Erythroid Ratio	
					Pronormoblasts	Basophilic Normoblasts	Polychromatic and Orthochromatic	Total	Promyelocytes and Myelocytes	Metamyelocytes (Juvenile Forms)	Segmented Forms	Total		
1‡ Male 46	On admission	11.8	8.34	73										Symptomatic and hematologic relapse at 3 months. Second course given.
	After phlebotomy	7.8	5.40	55	0.6	2.4	30	33	13.7	24.2	22.4	60.3	1.8:1	
	At 24 hours				0	0.2	31.8	32	14	26.6	23.8	64.4	2.0:1	
2‡ Male 45	On admission	11.3	7.33	80										Symptomatic and hematologic remission continuing at 6 months.
	After phlebotomy	7.4	4.18	53	1.2	1.6	21.2	24	12.8	27.6	29.8	70.2	2.9:1	
	At 48 hours				0	0.4	14.6	15	8.4	34.4	34.2	77	5.1:1	
	At 72 hours				0	0	4.6	4.6	8.2	39.6	41.2	89	19:1	
3‡ Female 57	On admission	9.0	8.47	78										Asymptomatic, hematologic relapse at 5 months. Second course given.
	After phlebotomy	10.6	6.44	58	0	0.8	27.6	28.4	16.2	18.2	20.2	54.6	1.9:1	
	At 24 hours	6.95			0	0	27.4	27.4	14.4	23	22.2	59.6	2.2:1	
	At 96 hours	5.36		52	0	0	23.8	23.8	15.2	23.6	24.2	63	2.6:1	
	At 3 weeks	4.8	4.64		0	0	14.4	14.4	20.4	26.8	26.2	73.4	5.1:1	
	At 5 months	5.9	5.39	56	0.4	2.4	38	40.8	14.2	25	13.6	52.8	1.3:1	
4§ Male 51	On admission	7.2	9.39	84										Symptomatic and hematologic relapse at 3 months. Second course given.
	After phlebotomy	9.1	4.82	55	0.4	2.6	27.8	30.8	6.2	25.6	20.2	52	1.7:1	
	At 48 hours	10.2	4.85		1	1.4	45	47.4	10.8	20	7.2	38	0.8:1	
	At 96 hours	8.6	4.90		0	0.2	13.2	13.4	8.2	26	34.8	69	5.1:1	

TABLE 1—*Continued*

Case, Sex, Age, yrs.	Interval after Beginning Treatment*	Leukocytes, thousands per cu. mm.	Erythrocytes, millions per cu. mm.	Vol. Packed RBC, c.c. per 100 c.c. Blood	Pronormoblasts	Basophilic Normoblasts	Polychromatic and Orthochromatic	Total	Promyelocytes and Myelocytes	Metamyelocytes (Juvenile Forms)	Segmented Forms	Total	Myeloid: Erythroid Ratio	Period Followed and Clinical Course after Treatment
5‡ Male 64	On admission	12.5	6.26	62										Symptomatic and hematologic remission continuing at 5 months.
	After phlebotomy		5.0	47	0	1.4	19.8	21.2	14.8	26.6	19.4	60.8	2.9:1	
	At 120 hours		4.31		0	0	2	2	5.8	28.2	41.2	75.2	38:1	
6§ Female 61	On admission	6.5	7.8	61	1.2	2.2	38.4	41.8	14	22.8	8.8	45.6	1.1:1	Symptomatic and hematologic remission continuing at 2 months.
	No phlebotomy	5.4												
	At 120 hours	6.3	8.11	83	0	0	6.2	6.2	8	35.2	33.6	76.8	12:1	
7 Female 57	On admission													Symptomatic and hematologic remission continuing at 2 months.
	After phlebotomy			58	1.8	2.4	52.4	56.6	9.6	21.6	5	36.2	0.6:1	
	Marrow not obtained after treatment													
8 Male 55	On admission	7.0	7.0	66										Symptomatic and hematologic remission continuing at 14 months.
	After phlebotomy	6.3	6.9	61	0	1.2	27.8	29	14.8	35.4	12	62.2	2.1:1	
	Marrow not obtained after treatment													

* Time indicated in hours represents time elapsed between initial injection of nitrogen mustard and sternal aspiration. Values "after phlebotomy" are those obtained just prior to initial injection of nitrogen mustard.

† Figures represent percentage of each cell type in a total of 500 nucleated cells.

‡ Received 2 injections of 0.2 mg. per kilogram each on successive days.

§ Received 4 injections of 0.1 mg. per kilogram each on successive days.

In making the differential counts in each case, an area was selected in the thinner portion of the smear where an even distribution of cells was apparent, and a total of 500 nucleated cells was counted. The myeloid-erythroid ratios shown in table 1 were obtained by dividing the total number of granulocytes of all ages by the total number of nucleated erythrocytes of all ages in each case. The figures given for the various types of bone marrow cells in table 1 represent the percentages of each cell type in a total of 500 nucleated cells. Myeloblasts were not included in the calculations, since in no instance did they represent more than 1 per cent of the total count.

General Consideration of Bone-Marrow Findings

Polycythemia vera is a disease of such chronicity that, in many cases, it runs a course of many years.[6] For this reason, it is logical to assume that the increase of mitotic activity in the erythropoietic cells is of relatively small degree and not of an order which would result in such marked distortion of the bone marrow pattern as is seen, for instance, in myelogenous leukemia. The frequent findings of leukocytosis, due to increase in circulating granulocytes, and "left shift" in the granulocytic series, in association with the erythremia, have led to the view that both myeloid and erythroid hyperplasia occur in the bone marrow in many cases of polycythemia vera, the increases so balancing each other that the ratio of the different types of bone-marrow cells to each other does not depart markedly from the normal. Wintrobe[7] has subscribed to this view, stating further, however, that the percentage of nucleated red cells in the bone marrow may be moderately elevated. These studies of the bone marrow in this disease tend to confirm this latter statement.

As a general working rule, the myeloid:erythroid ratio in normal bone marrow is said to be 4:1 or 5:1. According to the very complete survey by Osgood and Seaman[8] of the reported studies on the cellular composition of normal bone marrow, the ratio of granulocytic cells to nucleated erythroid cells in the marrow of normal human adults approximates 3.67:1. Reference to table 1 will show that in the pretreatment marrow specimens of the patients comprising this study, the myeloid:erythroid ratio was invariably lower than that given by Osgood and Seaman, indicating a moderate increase over normal in the proportion of erythroid cells in most of these cases. However, it appears that in some patients with polycythemia vera the erythroid hyperplasia may be very marked, resulting in reversal of the myeloid:erythroid ratio, as indicated in table 1 for case 4 (at 48 hours) and case 7 (before treatment).

The increase in the erythropoietic activity in the pretreatment marrow specimens of the patients discussed here was seen to be due almost entirely to an increase in polychromatophilic normoblasts. A marked "shift to the left" in the erythroid series was not apparent in any case. There was no striking shift in the myeloid pattern in any of the same preparations. No

conclusions could be reached from observation of the mitotic figures in these smears, since in a good many instances the type of cell undergoing mitosis could not be identified positively.

Studies [9] on the mitotic activity of normal adult human bone marrow, obtained by sternal aspiration, revealed that the proportion of dividing erythroid cells to dividing myeloid cells was 55 : 45. In the production of the granulocytes, cells participating in division were 97 per cent myelocytes and 3 per cent myeloblasts. In the erythroid series, 9 per cent of dividing cells were early, and 91 per cent were late, mostly polychromatophilic, normoblasts.

Because of the predominance of polychromatophilic normoblasts and the relative scarcity of orthochromatic forms in the smears of all the cases presented in table 1, these two cell types were grouped together. Because of their functional relationship and their predominance in mitotic activity, promyelocytes and myelocytes were also grouped together.

EFFECTS OF NITROGEN MUSTARD ON CELLULAR COMPOSITION OF BONE MARROW

It is not intended to stress the absolute values for the different cell types in table 1, but it is believed that certain obvious trends may be significant. Because the mitotic activity of the bone marrow in these cases is represented, in very large measure, by the values for polychromatic and orthochromatic normoblasts and for promyelocytes and myelocytes, the changes in these columns, along with the changes in the myeloid : erythroid ratio, are believed to reflect the major early changes in the cellular composition of the bone marrow as a result of nitrogen mustard therapy.

The figures suggest that the reduction in the number of cells of the erythroid series is proportionately greater than that in cells of the granulocytic series up to the end of 120 hours after the beginning of treatment, or as late as three weeks after treatment in case 3. Although the percentage of pronormoblasts and basophilic normoblasts was never strikingly increased before treatment, the decrease in the percentage of these immature cells apparently is an early result of the administration of nitrogen mustard. In the cases in which therapy resulted in the greatest reduction in the percentage of normoblasts (cases 2, 5, and 6), concomitant reduction in the percentage of promyelocytes and myelocytes occurred, but in no case was this of an order strictly comparable with the depression of the erythroid series. In cases 3 and 4, in which less marked reduction of the percentage of normoblasts occurred, the percentage of promyelocytes and myelocytes was not reduced, either at the end of 96 hours after the initial injection in case 4 or as late as three weeks after treatment in case 3. The early effects of nitrogen mustard on the relative numbers of cells concerned with mitosis in the erythroid and myeloid lines in cases 2, 4, 5 and 6 are charted in figure 1.

The values for cases 1 through 6 in table 1 indicate that significant re-

duction in the percentage of normoblasts may occur between 24 and 48 hours, and the reduction may become marked between 48 and 72 hours, after the initial injection of nitrogen mustard.   There is some indication that a significant reduction in the percentage of normoblasts may take place in the absence of marked general hypoplasia of the bone marrow, or that it may,
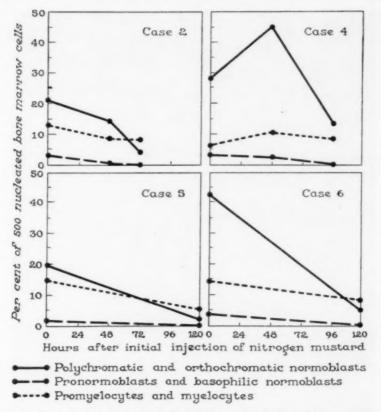
Fig. 1. Percentage changes in the erythroid and myeloid cells predominant in mitotic
activity up to 120 hours after the beginning of nitrogen mustard therapy.

on the other hand, be merely a part of such general hypoplasia.   The photomicrographs in figure 2 help to illustrate this point.   The reproductions of the marrow patterns shown for case 4 (figures 2a and 2b) indicate remarkably little change in the overall cellularity of the marrow during a period when a significant decrease in the percentage of normoblasts was taking place.   This finding and the subsequent course of this patient, with

hematologic relapse three months after the initial course of nitrogen mustard, suggest that significant general hypoplasia of the bone marrow did not occur.

In case 6 (figures 2c and 2d), on the other hand, marked reduction in the percentage of normoblasts at the end of 120 hours after the initial injection was seen to be associated with a marked general hypoplasia of the bone
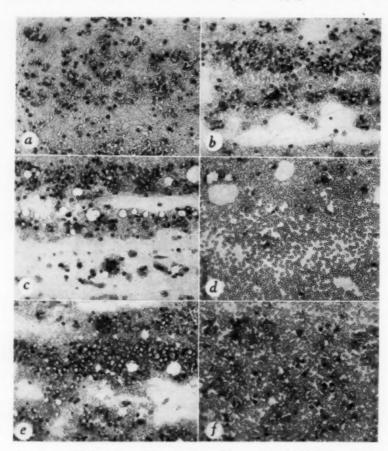
Fig. 2. *a* and *b* (case 4). *a*. Marrow pattern 48 hours after initial injection of nitrogen mustard (course one-half completed). Percentage of erythroid cells 47.4. *b*. Ninety-six hours after initial injection (24 hours after completion of course). Percentage of erythroid cells 13.4. General hypoplasia has not occurred. *c* and *d* (case 6). *c*. Before treatment. Percentage of erythroid cells 41.8. *d*. One hundred twenty hours later (48 hours after completion of treatment). Percentage of erythroid cells 6.2. Marked hypoplasia of the marrow. *e* and *f* (case 5). *e*. Before treatment. Percentage of erythroid cells 21.2. *f*. One hundred twenty hours later (96 hours after completion of treatment). Percentage of erythroid cells 2. Moderate general hypoplasia of the marrow (All × 100).

marrow.   That the hypoplasia continued in this patient was indicated by a report from her home physician which stated that leukopenia (1,000 leukocytes per cubic millimeter of blood), neutropenia (24 per cent neutrophils), and purpura were present in the third week after completion of treatment. No platelet count was reported at that time.   Anemia was not apparent, the erythrocytes numbering 5,500,000 per cubic millimeter of blood.   Approximately two weeks later, according to the home physician's report, the leukocytes numbered 4,300, the erythrocytes 5,100,000, and the platelets 209,000 per cubic millimeter of blood, and the differential count showed 61 per cent neutrophils; the patient's condition was satisfactory.   This was the only patient among the 11 treated with nitrogen mustard in whom marked
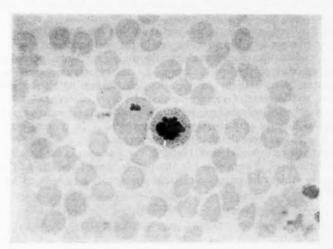
Fig. 3.   Nuclear fragmentation and basophilic stippling in polychromatic normoblasts from case 5, 120 hours after the beginning of treatment (× 900).

leukopenia or purpura occurred insofar as our follow-up data are informative.

In case 5 (figures 2e and 2f), changes in the marrow pattern after treatment suggested that a marked decrease in the percentage of normoblasts was associated with a moderate general hypoplasia, a condition which appeared to stand midway between those found in case 4 and in case 6.   Follow-up data in case 5 did not show marked leukopenia or thrombocytopenia, and the blood counts were normal five months after the treatment was completed. In case 3, the marrow patterns after treatment were very similar to those in case 4, while those in case 2 were similar to those in case 6.   In case 1, no marked change in the overall marrow pattern was apparent 24 hours after the initial injection; the percentage of the most immature erythroid cells had decreased to a degree similar to that noted in the other cases.

Morphologic changes attributed to the action of nitrogen mustard on polychromatic and orthochromatic normoblasts were in the form of Howell's bodies, either single or multiple, pyknosis, multiple nuclear fragments and coarse basophilic stippling.   Aside from occasional basophilic stippling, none of these changes was noted in any of the pretreatment specimens of marrow. These changes in the normoblasts were not apparent in the specimens obtained at 24 hours after the initial injection, were noted first in those obtained at 48 hours, and were most marked in those obtained at 96 and 120 hours. In cases 5 and 6, the majority of normoblasts in the 120 hour smears showed one or more of these abnormalities.   Representative of some of these changes are those in the polychromatic normoblasts shown in figure 3.   In case 3, only an occasional Howell body was observed in polychromatic normoblasts in the marrow obtained three weeks after treatment; none of the other changes mentioned previously was noted in that specimen.

Toxic changes noted in granulocytes in the post-treatment smears consisted of condensation of nuclear chromatin, toxic granulation, partial loss of staining reaction of the specific granules, and cytoplasmic vacuoles.   In lymphocytes, vacuolization, condensation of chromatin, altered staining reactions, and increase of azurophilic granules were observed.

The number of megakaryocytes in the post-treatment marrow preparations varied directly with the degree of hypoplasia.   In no case were they found to be absent from the post-treatment smears.

Phagocytic reticulo-endothelial cells, of the type seen in the bone marrow in hemolytic disease, were noted in the post-treatment smears, particularly in those in which the effects of nitrogen mustard were seen to be most marked.

COMMENT

A protracted period of investigation will be necessary before the value of nitrogen mustard in the treatment of polycythemia vera can be adequately assessed and compared with that of the other methods of treatment.

No statement is warranted, on the basis of this study, in regard to the ability of nitrogen mustard alone to maintain remissions in this disease, since phlebotomy was performed in all but one case and an adequate follow-up period has not elapsed.   From the standpoint of clinical results, the facts relative to the 11 patients treated so far may be briefly summarized as follows: Three patients relapsed between three and five months after their initial treatment and received a second course of nitrogen mustard.   The values shown in table 1 for case 3 "at 5 months" were obtained from a marrow specimen taken just prior to the beginning of a second course of treatment.   They indicate a return to the pretreatment bone marrow pattern, with evident erythroid hyperplasia.   Eight patients, including three who were not a part of this study, were in hematologic remission and free of symptoms at periods varying from two to 14 months after their initial treatment.

The dosage and dosage schedules employed in the routine use of nitrogen mustard therapy were designed primarily for the treatment of diseases other than polycythemia vera, and the nature of those diseases is such that a therapeutically effective dose will of necessity be potent enough to cause marked hypoplasia of the bone marrow in many cases.   This may not be true for polycythemia vera.   It is a matter deserving further study.

The bone-marrow pattern in uncomplicated polycythemia vera is characterized by a variable degree of erythroid hyperplasia, occurring in an orderly fashion, and therefore it does not deviate widely from the normal. In such a situation, to produce severe hypoplasia of the entire bone marrow is not a desirable therapeutic effect, and such a result, coming on as rapidly as it sometimes does after administration of nitrogen mustard, must represent not only suspension of mitotic activity but injury and disintegration of the resting hematopoietic cells as well, as pointed out by Friedenwald and co-workers.[3]   Such effects should be minimized if possible.   It has become obvious that among different patients the susceptibility of the hematopoietic cells to the effects of nitrogen mustard varies considerably.   Attempts to individualize dosage and dosage schedules, with this variable factor in mind, should be made.

Some of the findings derived from the cases discussed here suggest that in polycythemia vera the effect of nitrogen mustard on erythropoiesis is relatively greater than on myelopoiesis, and that significant reduction in the percentage of erythrocyte precursors may occur after this treatment without marked general hypoplasia of the marrow.   These findings may not be peculiar to polycythemia vera.   However, they suggest that in patients with polycythemia vera it would be profitable to investigate the use of smaller doses of nitrogen mustard, perhaps repeated, if necessary, at shorter intervals than has been the custom, with the aim of finding a dosage schedule which may result in adequate depression of mitosis in the erythropoietic cells without producing severe or prolonged hypoplasia of the bone marrow generally. The possibility of variable effects resulting from different dosage schedules, under experimental conditions, has been alluded to by Karnofsky and co-workers.[10]   Further observations on the bone marrows of patients with polycythemia vera and other diseases who are receiving nitrogen mustard therapy will be of primary value in determining the most rational plan of treatment.

As has been the custom with radiophosphorus therapy of polycythemia vera, phlebotomy should be employed initially only to the point of obviating severe symptoms or imminent complications, avoiding reduction of the erythrocyte count by this means to less than 6,500,000 per cubic millimeter of blood, in order that the effect of nitrogen mustard may be assessed more easily.   A reëvaluation of the hematologic status may be made six to eight weeks after the initial course, and supplementary treatment may be given at that time if indicated.   Subsequent treatment may be given as dictated by periodic examinations and the clinical course.

Nitrogen mustard must meet certain fundamental requirements in order to qualify as a suitable agent for the treatment of polycythemia vera. First, it must be demonstrated that, the erythrocyte count and volume of packed erythrocytes having been returned to normal by the initial treatment, nitrogen mustard alone has the ability to maintain these normal values. Second, it must control erythremia without unduly depressing the numbers of circulating leukocytes and platelets. Third, it must be shown that the toxicity of nitrogen mustard does not preclude its routine use over such long periods as are required for the treatment of polycythemia vera.

SUMMARY AND CONCLUSIONS

This report includes a study of the cellular composition of the bone marrow, before and after nitrogen mustard therapy, in eight patients with polycythemia vera. A variable degree of erythroid hyperplasia was apparent in the pretreatment bone marrow specimens, the ratio of myeloid to erythroid cells varying from 0.6:1 to 2.9:1. Significant shifts toward immaturity in the erythrocyte and granulocyte precursors were not observed.

Some indications were elicited that the effect of nitrogen mustard was proportionately greater on erythropoiesis than on myelopoiesis in these patients.

Significant reduction in the percentage of normoblasts may occur between 24 and 48 hours, and may become marked from 72 to 120 hours after the initial injection of nitrogen mustard, with progressive parallel decrease of the most immature cells of the erythroid series. When the reduction in the percentage of normoblasts was most marked, it was seen to be a part of a general hypoplasia of the bone marrow, but significant reduction in the percentage of erythrocyte precursors may occur in the absence of marked general hypoplasia.

It is hoped that further investigation will make possible a plan of treatment for polycythemia vera, utilizing different dosage of nitrogen mustard and different dosage schedules than have been customary, taking into account the differences, among various patients, in susceptibility of the hematopoietic cells to the drug. The objective is to produce adequate depression of erythropoiesis without severe general hypoplasia of the bone marrow, thus increasing the safety with which nitrogen mustard may be employed in the treatment of this disease.

It has yet to be demonstrated that nitrogen mustard meets the requirements which would qualify it as a suitable agent for the routine treatment of polycythemia vera.

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ADRENAL CORTEX IN LIVER DISEASE *

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This paper reports our experience in the treatment of liver disease using a new therapy : extract of adrenal cortex.

We have felt for some time that forced feedings of proteins and carbohydrates with high vitamins as suggested by Patek,[1] intravenous human serum albumin,[2] and the use of lipotropic compounds were in large part an effort to support the patient until the liver repaired itself. Too often these measures failed. Watson[3] has recently emphasized "the difficulties in the prognosis and treatment of hepatic disease, difficulties which are inherent because of the multiplicity of the functions of the liver, the remarkable dissociation of functional impairment encountered in disease, and the liver's ability to regenerate in spite of severe injury." He has said that we must freely admit that our ability to treat liver disease on any rational basis has made but little progress in the centuries since Hippocrates.

Our hope was to find a substance which would alter the metabolism of carbohydrate and protein so as to protect the liver and encourage reparative processes. It seemed that one which would also increase the storage of hepatic glycogen might do this. We think that adrenal cortex extract achieves these aims.

Many investigators have studied the physiologic changes in carbohydrate and protein metabolism effected in experimental animals by whole adrenal extracts and pure steroids. Some have studied humans suffering from disease of the adrenal glands. We have been able to apply their conclusions directly to our patients, and have attempted explanation of certain undesirable but expected effects, such as glycosuria and diabetic glucose tolerance curves.

Review of the Literature

The adrenal cortex is necessary to life. Stewart and Rogoff[4] administered adrenal cortex extract and saline to adrenalectomized animals and prolonged their lives. Hartman[5] gave the name "cortin" to such an extract. Britton and his coworkers[6] found that liver, muscle, and blood carbohydrate and liver glycogen, reduced in adrenalectomized animals, were restored by cortical extracts. Blood sugar and liver glycogen of normal animals were also increased by such treatment. Long, Katzin and Fry[7] noted similar effects in fasting or adrenalectomized animals. Because of increased nitrogen excretion, it was believed that the gluconeogenesis was due to protein catabolism. Albright and his coworkers[8] have also demonstrated that the adrenal hormones enhance the rate and extent of protein breakdown. Wells

and Kendall[9] decided that adrenal cortex was chiefly concerned with the breakdown of tissue protein to amino acids, but not directly with the conversion to glycogen, since the adrenalectomized animal continues to deposit some glycogen in the liver. Corey and Britton,[10] working with the isolated liver, concluded that the adrenal cortex extract favors glycogenesis in the liver.

Long and Lukens[11] removed the adrenals of depancreatized animals, thus reducing their diabetes. When Lukens and Dohan[12] administered cortical extracts to such animals their diabetes was increased. Britton and Silvette,[6] Zunz and LaBarre,[13] and Zwemer and Sullivan[14] obtained rises of blood sugar on administration of cortical extracts to normal animals. Koepf, Horn, Gemmill and Thorn,[15] in studies on rat liver slices, found that adrenal cortical hormone increased the rate of carbohydrate synthesis from pyruvate and d-lactate. Wells and Kendall,[9] Ingle and Thorn,[16] and Long[17] felt that the adrenal cortex interferes with peripheral utilization of glucose by the tissues. It has been found in adrenalectomized animals that the slow absorption of sugar, fat and poor glycogen formation may be influenced by the administration of salt and carbohydrate (Allen), and that such animals cannot fully work or endure stress without cortin.

The adrenal steroids which seem to have the most direct effect on carbohydrate metabolism are the corticosterones: corticosterone isolated by Reichstein and his coworkers, 11-dehydrocorticosterone (Kendall's A compound), and 11-dehydro-17-hydroxycorticosterone (Kendall's E compound, Reichstein's Fa6, cortisone). These favor gluconeogenesis and glycogen deposition chiefly from protein by aiding in the deaminization of amino acids or changing keto and hydroxy acids to carbohydrate. They influence the oxidation of glucose in the tissues, postpone muscular fatigue, and exert a glycotropic or anti-insulin effect. They restore carbohydrate levels and glycosuria of partially depancreatized or adrenalectomized, partially depancreatized animals (Long et al.). In large doses, these hormones with oxygen at position 11 cause glycosuria, ketonuria, and increased excretion of nitrogen, phosphorus and potassium in partially depancreatized rats. Best and Taylor[18] state that these adrenal compounds are very powerful diabetogenic agents. Many of the aforementioned hormonal effects have been noted during the use of cortisone by Hench, Kendall and their coworkers[25, 26] in rheumatic fever and rheumatoid arthritis. On the other hand, even after enormous doses of cortisone, in only a few cases has there been any elevation of the blood sugar in the fasting condition, and never glycosuria.[31]

The evidence of carbohydrate effects has been supported by studies of patients suffering from adrenal disease. Lukens and his group[19] analyzed 55 cases of adrenal cortex tumor and hyperplasia. They found no impairment of carbohydrate metabolism in 28, but 19 had glycosuria, and eight had deficient carbohydrate utilization as seen by glucose tolerance curves. Kepler and Wilder[20] found abnormal carbohydrate metabolism in four

patients, and diabetes in one of eight persons with adrenal cortex tumors. In patients suffering from Addison's disease, the bromsulfalein test was noted to be impaired by Rowntree and Snell,[21] indicating liver dysfunction. Using intravenous hippuric acid in nine patients with Addison's disease, Thorn, Dorrance and Day [22] found all had low values. Hartman [23] has stated that the whole question of carbohydrate storage, glyconeogenesis and carbohydrate and fat oxidation may be concerned with metabolic disturbances of the liver, and that changes may become serious only when continued over a long period or when stress creates an unusual demand.

METHOD AND MATERIAL

Because the liver has remarkable recuperative powers and because the prediction of outcome of any case of liver disease is difficult, we chose nine patients, all of whom had received the usual therapy and continued a downward course. The diseases were: cirrhosis (4), homologous serum jaundice (1), chronic active infectious hepatitis (1), chronic hepatitis with "pseudo colic" (1), and arsenical hepatitis (2).

In May, 1948, we began looking for a supply of corticosterone or Kendall's E compound. These were not available, but Dr. E. C. Kendall, of the Mayo Clinic, gave us some of his aqueous adrenal cortex extract with suggestions as to the dosage necessary to alter the carbohydrate metabolism. Later we obtained an aqueous adrenal cortex extract practically free of medulla hormone. On Cartland-Kuizenga assay,[24] each cubic centimeter contained 2.5 to 3.0 rat survival units, or 50 to 60 dog units. It equaled 0.4 mg. to 0.5 mg. of corticosterone and affected the carbohydrate and protein metabolism. We then secured an oil extract of the adrenal cortex which was the equivalent of 4.0 to 4.5 mg. of corticosterone, or 2.0 to 2.5 mg. of 11-dehydro-17-hydroxycorticosterone.

During the course of therapy, patients were encouraged to eat proteins and carbohydrates and were asked to abstain from alcohol. We maintained the treatment already instituted in each case, adding only the adrenal cortex extract.

CASE REPORTS

Case 1. This was a 27 year old man suffering from a recurrence of hepatitis with severe parenchymal damage, first contracted in 1942 while serving in the Army. He had frequent attacks, one of which necessitated a four-month bed rest. He had fever, sweats, weight loss, jaundice, marked drowsiness and hepatosplenomegaly. The pertinent laboratory findings were: white cells, 12,900, with a shift to the left; icteric index, 60; Hanger test, 3 plus; albumin, 3.0; globulin, 2.5; prothrombin time, 20 per cent of normal.

When the patient did not respond to four weeks of bed rest, nutritious diet, blood transfusions, lipotropic substances, parenteral fluids, liver, and vitamin K, and appeared semicomatose, 10 c.c. aqueous adrenal cortex extract was administered daily. One week later the man's temperature was normal, he was alert and hungry, and his jaundice was obviously decreasing. At the end of two weeks' further therapy, he had

gained 18 pounds and appeared well. After cessation of treatment, the patient lost five pounds in three days due to marked diuresis. A month later he was 10 pounds heavier, laboratory tests were normal, and his liver and spleen were not palpable. A year later, although he was working as a truckman and drinking almost a quart of wine daily, he was well and had had no recurrence of his illness.

Case 2. This 56 year old man, a chronic alcoholic, was considered moribund when first seen. He had had peripheral neuritis for nine years, cirrhosis for at least two years, and had just left a New York hospital where he had been treated for four months with the Patek nutritious diet and vitamin supplements, parenteral blood, serum albumin, and diuretics, without success. He had weight loss, fever, fetor hepaticus, deep jaundice, generalized edema, abdominal ascites, hepatosplenomegaly, marked lethargy, spider angiomata, and gum and tongue hemorrhages. Hemoglobin after transfusion was 40 per cent; icteric index, 80; prothrombin, 10 per cent of normal; cephalin flocculation, 3 plus; thymol turbidity, 7 units; albumin, 2.5, and globulin, 2.0. There was no hyperglycemia or glycosuria.

This patient received 10 c.c. aqueous adrenal cortex extract daily for 15 days, then 15 c.c. three times weekly for two weeks, and then weekly for three months. At the end of the first 10 days he was alert, hungry, and complained of his "enforced bed rest." Five days later his gum bleeding ceased and the sole bleeding area remaining was a fungating mass at the left side of the tongue. (Biopsy at the French Hospital and the Memorial Hospital confirmed the diagnosis of squamous cell carcinoma.) During the second week of therapy, urine analysis revealed 0.5 to 1.0 per cent sugar. At the end of a month he had gained weight and lost all edema and ascites. Despite intensive radiation therapy to tongue and neck at the Memorial Hospital, he did not feel weak or nauseous. In May, 1949, six months after cessation of therapy, he was admitted to the Polyclinic Hospital for further study. There was no ascites, and the liver and spleen were not palpable. Hemoglobin was 60 per cent; red cells, 3,000,000; bilirubin, 1.6; Hanger test, 1 plus; blood glucose, 129; albumin, 5.9, and globulin, 3.0. Roentgenogram revealed extensive metastases to the lungs. A month later the patient died of bronchopneumonia and metastatic carcinoma.

Case 3. This 54 year old man had had peripheral neuritis, cirrhosis, chronic alcoholism, and bouts of rheumatoid arthritis for six years. There was no family history of diabetes, and during four hospital admissions there had been no glycosuria or hyperglycemia. After a year of treatment with parenteral liver, diuretics, high carbohydrate-protein diet and lipotropic compounds, he had jaundice, ascites, mucous membrane bleeding, hepatomegaly, dark pigmentation of the face and neck, and loss of axillary hair. Laboratory studies were: cephalin flocculation, 3 plus; urea nitrogen, 21.5; icteric index, 22.5; albumin, 2.5; globulin, 3.0; cholesterol, 260; esters, 125; prothrombin time, 43 per cent of normal; glucose, 85. Urine contained no sugar.

In August, 1948, the patient received 10 c.c. aqueous adrenal cortex extract daily for 10 doses. On the fifth day, the blood pressure rose from 110 systolic and 60 diastolic to 160 systolic and 80 diastolic. The latter figure was maintained until treatment ceased. The tenth day jaundice was decreased, appetite was improved, and previously ineffective diuretics caused loss of six pounds daily. At this time he complained of precordial pain. Physical examination, orthodiagram, electrocardiogram, and other studies revealed no obvious abnormality of the heart. Fifteen c.c. extract were administered weekly for three months. All urinalyses were normal until February, 1949, when the patient complained of thirst, hunger, and urinary frequency. His urine contained 2 per cent sugar, and the fasting blood sugar was 200 mg. Hyperglycemia was controlled with difficulty by insulin and diet. In April, 1949, at the Polyclinic Hospital, there was no evidence of any hepatic disease but all urines contained sugar and the glucose tolerance curve was diabetic in type. At present the patient feels well except for renewed attacks of his rheumatoid arthritis.

He has an increase of the axillary hairs and decrease of the facial pigmentation. He takes insulin daily and Tolserol , which we found relieves his anxiety and need for alcoholic beverages.

Case 4. A 48 year old man with chronic ulcerative colitis for 23 years had homologous serum jaundice three months after a blood transfusion. He had fever, deep jaundice, bloody diarrhea, nausea, and a large tender liver. Icteric index was 65; alkaline phosphatase, 25 Bodansky units; prothrombin time, 40 per cent of normal; Hanger test, 4 plus; urine urobilinogen, 20 mg. in 24 hours. In spite of parenteral glucose, blood, vitamin K, and a high protein-carbohydrate diet for two weeks, the fever continued to rise and laboratory tests indicated progression of the disease.

Five c.c. adrenal cortex oil extract were administered daily; 48 hours later, the patient was more alert and "ravenously hungry." At 96 hours the temperature was normal and he seemed euphoric. He felt "all well." After five daily doses, the medication was reduced to 2 c.c. daily for one week and then to 1 c.c. daily for another week. On the twentieth day the liver was not palpable and the prothrombin time was normal. A month later, laboratory tests were normal, diarrhea had ended, and sigmoidoscopic examination revealed only a few pinpoint ulcerations. In November, 1948, because of renewed diarrhea and faint icterus, the man was hospitalized and received 5 c.c. aqueous adrenal cortex extract for 10 days. At the end of that time jaundice had left, diarrhea had ceased, and examination revealed healing mucous membrane. The patient has had no recurrence of liver or bowel dysfunction for the past year.

Case 5. This 65 year old female had had bilateral mastectomy for carcinoma 20 years ago. Because of painless jaundice, she had surgical exploration and ductal studies in 1947. The liver was enlarged, soft and deeply pigmented; a fibrotic, non-calculous gall bladder was not removed. Since the operation the patient had had dizziness, fever, and frequent attacks of painful jaundice. Blood sugar was 100; cholesterol, 201; esters, 122; urea nitrogen, 27.2; bilirubin, 3.8; thymol turbidity, 8 units; Hanger test, 3 plus.

After two months' treatment with parenteral liver, high protein-carbohydrate diet, and lipotropic compounds, the "pseudo gall stone colic" and parenchymal liver damage seemed unchanged. Ten c.c. adrenal cortex aqueous extract were administered daily for 10 days. On the seventh day the patient began to eat ravenously, complaining that she was being starved. She received 5 c.c. three times weekly for another 21 days. At this time medication was withdrawn because she appeared manic, reacted violently to her physician and family, and complained of precordial pain. There were no changes in her cardiac status as determined by examination, orthodiagram, and electrocardiogram; jaundice had disappeared; the liver was no longer palpable, but the blood glucose was 148 and the urine contained a trace of sugar. Twenty-four hours after medication was discontinued, the personality reverted to normal, precordial distress was relieved, and there was no evidence of glycosuria. The blood sugar reverted to the former level. A year later the patient returned for recheck, complaining of rheumatoid arthritis. Liver function studies, including glucose tolerance test, were all normal.

Case 6. A 34 year old man came for further care from Puerto Rico, where he had been confined to a hospital for three months because of hepatitis following two injections of salvarsan. He was faintly jaundiced, emaciated, drowsy and had a large tender liver. Serum bilirubin was 8 mg.; albumin, 3.3; globulin, 2.0; alkaline phosphatase, 10 Bodansky units; sedimentation rate, 44 mm. in one hour; blood and spinal Wassermann tests, negative for syphilis; colloidal gold test, normal.

Because he did not improve after three weeks' treatment with a high carbo-hydrate-protein diet and vitamin supplements, parenteral liver and other supportive therapy, the patient was given 10 c.c. aqueous adrenal cortex extract for only 10

days. The third day he felt better and his liver was less tender. Four weeks after the 10-day course of adrenal cortex therapy he was evidently well, laboratory tests were normal, and the liver was not palpable. A year later the patient was seen for acute alcoholism. There was no evidence of any residual liver disease, and Tolserol® and abstinence were advised.

Case 7. This 57 year old man had a history of jaundice and fever four years ago following a course of penicillin and arsenic for primary seronegative syphilis. He had been reinfected, had a new chancre, and received a course of penicillin and Mapharsen®. He was jaundiced, had a "new mown hay" breath, an extremely tender, enlarged liver, and a healing chancre. Bilirubin was 16.0; thymol turbidity, 16 units; cholesterol, 200; esters, 20; alkaline phosphatase, 12 units; albumin, 2.5; globulin, 3.0; Wassermann, Mazzini, and VDRL tests strongly positive. Intravenous glucose, plasma, high protein-carbohydrate diet with vitamin, and lipotropic supplements sustained the patient for nearly two weeks.

When the serum bilirubin continued to increase and the cholesterol esters decreased 15 c.c. adrenal cortex oil extract were given daily. After seven days, fetor hepaticus disappeared and the patient seemed stronger. Treatment was continued with 2 c.c. every other day for three weeks. During this time jaundice diminished, the liver decreased, and facial and ankle edema were noted but not considered sufficient to stop the medication. One month after cessation of therapy the thymol turbidity was 8 units. Two months later all tests were normal. Recheck in a year revealed no evidence of liver disease.

Case 8. This 48 year old man had had cirrhosis for two years and weakness, impotence, loss of body hair, and hypertension for one year. His mother had died of diabetes. He had icterus, ascites, hepatomegaly, and ecchymoses. Pertinent laboratory data were: serum bilirubin, 2.5; cephalin flocculation, 3 plus; albumin, 3.0; globulin, 2.5; cholesterol, 200, and esters, 80; glucose, 80; prothrombin time, 20 per cent of normal. The patient continued his downward course after three weeks of a high protein-carbohydrate diet, intravenous liver, vitamin K, glucose, and diuretics.

Ten c.c. oil adrenal cortex extract were administered daily for 10 days, then three times weekly for two weeks. On the tenth day the patient felt fine and there was no jaundice or bleeding. The blood pressure did not increase. One month later the patient was admitted to the Polyclinic Hospital for study. He had no jaundice and no liver enlargement, and function tests were normal. Reëxamination the following year revealed new growth of body hair and normal liver tests, although he had been drinking heavily for the past six months. He stated that he was no longer impotent.

Case 9. This patient, a 54 year old man with a history of malaria and yellow fever, had had cirrhosis for two years. There was drowsiness, jaundice, loss of weight and hepatomegaly. Icteric index was 32; Hanger test, 8 units; albumin, 2.5; globulin, 2.0; cholesterol, 220, and esters, 100. The patient had received a high protein-carbohydrate diet with vitamins, parenteral liver, glucose, and diuretics for four weeks without improvement. Serum albumin was tried without success.

Five c.c. oil extract of adrenal cortex were given daily for 10 days. On the seventh day the patient was alert and hungry; the tenth day, fever and jaundice were gone. In two weeks there were no abnormal findings. One year later there was no liver dysfunction. Three weeks after his last examination the patient died suddenly of coronary thrombosis.

COMMENT

We have noted that the prognosis of diseases of the liver is extremely difficult. It was for this reason that we chose patients who, despite ac-

cepted therapy (total rest, high carbohydrate-protein diet, vitamin and lipo-
tropic supplements, blood transfusions, intravenous liver, plasma, serum
albumin, glucose, diuretics, and salt restriction), were rapidly going down-
ward.

The fact that all of our patients survived and, on the whole, did well is
probably of no statistical importance because of the small number treated.
It is of importance, though, that their survival and rehabilitation followed
the introduction of one new therapeutic measure—adrenal cortex extract.

In this day of determinate therapy, the use of a crude mixture of many
steroids and an active amorphous substance [27] seems an anachronism.
Nevertheless, since single active agents like corticosterone and the E and F
compounds of Kendall will probably not be available for wide distribution
for years, it is unfair to withhold possible help to the patient or experience
to the physician.   It was necessary to stop medication only once (Case 5).
Because of the multiple nature of our drug we expected sodium and fluid
retention, alteration of blood and urine sugar, potassium excretion, glycogen
deposition, hypertension, and changes in the body hair.

Our patients were too ill to attempt liver biopsy, so that we could not
prove glycogen deposition by staining methods nor illustrate histologically
the dramatic clinical and chemical changes as we followed them.

Transient glycosuria was found in only two patients (Cases 2 and 3).
Case 5, with no family history of diabetes and no previous evidence of
abnormality of carbohydrate metabolism, became frankly diabetic after this
therapy and was controlled with difficulty.   The need for insulin is still
present a a year later, although smaller doses are now adequate.   It is in-
teresting to note that this same patient had hypertension, regained lost
axillary hair, lost some of his face and neck pigment, and had acne while
receiving adrenal cortex.   The duskiness of skin and loss of axillary hair in
this cirrhotic patient may have been due to adrenal insufficiency as described
by Watson.[28]   Adrenal cortex probably acted as specific therapy on the one
hand, but caused possible permanent alteration in carbohydrate metabolism
on the other.   A year later only the diabetes remains of these Cushing
syndrome-like symptoms.

We expected edema due to retention of sodium and water.   Ascites when
already present did not increase but apparently decreased; this was due to
better response to mercurial diuretics, which we noted about the seventh day.
Although there was never enough edema to terminate treatment, there was
some latent edema in all our patients.   All had some diuresis at the end of
therapy.   There was no decrease in serum potassium, but increased excre-
tion indicated withdrawal from the body cells.   On the whole, blood electro-
lyte and nitrogen studies were not consistent and varied from day to day
despite continued treatment.   This fact has been noted by other investi-
gators.   We therefore abandoned further balance studies.

Two patients (Cases 3 and 5) complained of precordial distress, which
left promptly when therapy was terminated.   Physical examination, electro-

cardiogram, orthodiagram and other studies revealed no evident abnormality of the heart or alteration of the blood volume. We have no explanation other than that undetectable changes may have been temporarily present in the coronary arteries or heart muscle.

Certain very striking subjective effects are revealed during adrenal cortex therapy. All patients comment on the increased psychic stimulation as manifested by alertness and a feeling of well-being. This was followed in some cases by euphoria; in others, by annoyance and irritability at ordinary hospital routine, or even by mania. Uncontrollable and almost insatiable hunger was seen in every case. Prompt reversion to the usual personality occurred within 24 hours of withdrawal of therapy.

Several of our patients had a history of rheumatoid arthritis. Although this was not a complaint immediately before or during the present illness, joint disability recurred shortly after cessation of adrenal cortex therapy.

All of our cases illustrate an important fact: in hepatic diseases, it may not be necessary to continue this very expensive therapy after the initial beneficial result has been attained. This seems unlike the pharmacologic effect of adrenal cortex extract in adrenal insufficiency, or even in the cortisone therapy of rheumatoid arthritis. It has been the usual experience that in these diseases relapse occurs when treatment is withdrawn. In rare instances only, the beneficial effects of cortisone seem to be more lasting. Here, as in our cases, a physiologic change may be postulated. One may conjecture that readjustment or alteration of the carbohydrate-protein metabolism may be the effective agency by which adrenal cortex extract or these steroids operate.

Remissions in ulcerative colitis have been reported with almost every drug. We were, therefore, skeptical on seeing the rapid response to adrenal cortex in our case of serum hepatitis and ulcerative colitis. When the colitis cleared again on a second course of therapy (and has not recurred), we felt this worth further study. We are now treating several patients with early cirrhosis and ulcerative colitis, but follow-up has not been adequate for reporting at present.

The liver is a bulwark by which the organism resists infection, intoxication, and other types of stress. Thus its maintenance is one of the prime objects of the body economy. It forms an integral part of the Selye adaptation syndrome.[29] The production of carbohydrate by glyconeogenesis from protein and the formation in the liver of α_2-globulin (hypertensinogen) occur in response to adrenal cortex stimulation. Sayers and Sayers[30] indicate that stress increases the use and consumption of corticoids. We believe that the introduction of adrenal cortex extract helps replenish or augment the needed hormone, thus maintaining a balance in the body's homeostatic mechanism.

The apparent early clinical improvement in long standing cirrhosis with what we have thought of as permanent pathological changes is remarkable. Liver function seems helped in toto. This is evident when we think of the varied changes necessary to affect such widely different tests as those in the

usual liver profile. We have been accustomed to seeing patients, long after clinical recovery, retain a positive Hanger or thymol turbidity test. After adrenal cortex therapy, even those tests rapidly reverted to normal. We can only conclude that the remaining liver cells have been directly stimulated to regenerate and repair damaged tissue; that the carbohydrate-protein metabolism has been favorably altered in some fashion so as to increase cell energy, perhaps by storage of glycogen or availability of circulating glucose, and that certain adaptive phenomena have been evoked to protect the organism.

Summary and Conclusions

This paper reports our experience in the treatment of liver disease using a new therapy: extract of adrenal cortex.

A first group of nine patients was chosen for trial of the drug. All nine (cirrhosis, 4; homologous serum jaundice, 1; chronic active infectious hepatitis, 1; chronic hepatitis with "pseudo colic," 1; arsenical hepatitis, 2) recovered promptly and laboratory tests rapidly reverted to normal after treatment. Reëxamination after a year revealed no evidence of liver dysfunction, even in those with a history of chronic liver disease.

In the treated cases there was evidently: (1) psychic stimulation; (2) alteration of the carbohydrate-protein metabolism with glyconeogenesis from protein, deposition of liver glycogen, possible formation in the liver of a_2-globulin (hypertensinogen), changes in blood and sugar levels; and (3) sodium and fluid retention with potassium excretion and changes in body hair and pigment. Of three patients with hyperglycemia, one had a Cushing-like syndrome with possible permanent diabetes; two patients had hypertension, two had unexplained precordial distress, and all had latent edema. There was remission of complicating ulcerative colitis in one case. The further use of the drug in colitis and the sprue syndrome is being investigated.

Adrenal cortex extract is available in aqueous and oil solutions. Care must be used in its administration. Unlike the reported experience with ACTH and cortisone, extract of adrenal cortex may be discontinued when recovery is noted. It is believed that this is evidence of a true physiologic effect, possibly in balancing an adaptive homeostatic regulating mechanism or in the actual regeneration and repair of damaged liver cells.

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THE QUESTION OF TRAUMATIC HEART DISEASE[*]

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In a socially enlightened age of compensation and disability insurance, the relation of trauma to disease requires careful analysis. Only too often the prospect of reimbursement induces the patient, subconsciously at least, to relate his symptoms to some incident of ubiquitous trauma. Unfortunately and also too often, the sympathetic physician uncritically accepts the cause-and-effect relationship suggested by the patient and may even report the case in the medical literature affirming this impression. In the field of cancer such uncritical acceptance of the influence of trauma has resulted in mistaken concepts, which are only recently being broken down by the vigorous and forceful opposition of leading authorities[1] whose opinions are based on scientific facts.

A similarly critical attitude also seems warranted in assessing the condition that has come to be known as traumatic heart disease. Kahn and Kahn,[2] who presented a simple and adequate classification of lesions and other effects produced in the heart by trauma, expressed a thorough comprehension of the difficulty involved in estimating the effects of an injury, particularly when there is distinct evidence of previous heart disease. Warburg[3,4] very laboriously collected a total of 261 cases of traumatic heart disease from the literature, including those he reported. Among them are a large number which are frankly doubtful, as well as many others with inadequate or unconvincing data. In others, due consideration seems not to have been given the rôle of strenuous effort, as opposed to trauma, in precipitating cardiac failure and coronary thrombosis in a heart which was already seriously diseased. In attempting to establish his thesis, Warburg seems to have been unduly impressed by a history of trauma, while he minimized or overlooked much more likely alternative explanations. Serious objections could be raised to the inclusion of 29 of 51 autopsied cases in which he considered the rôle of trauma in the causation of heart disease established beyond doubt. His subsequent analyses of this material can, therefore, scarcely be accepted without reservations. It is interesting to note that the author himself decided that 36 of the cases he had previously listed should be discarded as doubtful.[4] The fact remains, however, that in 76 of the 202 cases in the first series,[3] there is reasonable evidence to indicate the presence of traumatic heart disease or insufficient evidence to deny it.

Cardiac lesions or injuries resulting in prompt death, such as the penetrating wound or "blow-out" of sudden forceful compression occurring in

high speed accidents, are of medico-legal significance, and with recent ad-
vances in technical approach are a challenge to the surgeon,[7, 8] but they are
of little interest to the internist.   The latter is chiefly concerned with the
fortunately small group of patients whose cardiac symptoms are initiated or
augmented by a traumatic incident.   The position of the heart within a
rigid bony cage provides considerable protection from physical trauma, as
any pathologist can testify.   It explains Butterworth and Poindexter's
failure to find electrocardiographic changes when 35 boxers were examined
immediately after the bouts of a Golden Gloves tournament.   Without frac-
tures of the thoracic wall or penetration it is rare to be able to demonstrate
cardiac contusions at autopsy in cases of severe trauma resulting in death.
Glendy and White [10] found not a single instance of cardiac trauma in the
course of 7,600 autopsies at the Massachusetts General Hospital, although
many deaths were due to accidents.

Admitting its rarity, there is abundant evidence testifying to the occur-
rence of a cardiac lesion with non-penetrating injury.[11, 12, 13, 14, 15, 16, 17]   In
a pathologic study of 262 fatal accidents, Osborn [18] found nonpenetrating
traumatic lesions of the heart in 19.   The elasticity or flexibility of the
thorax may be a factor contributing to the likelihood of such lesions, as sug-
gested by Arenberg,[19] Sigler,[20] and Wilson.[21]   Even at autopsy, however,
it is difficult to distinguish traumatic from natural heart disease.   The
principal differential pathologic features Moritz and Atkins [22] observed were
the conspicuously disruptive and hemorrhagic character of the traumatic
lesions and the uniformity of the changes in various portions of the lesions,
indicating their common onset and duration.   The subsequent reactive
changes—leukocytic infiltration, absorption of necrotic tissue, and scarring
—were similar in many respects to myocardial infarction.   The authors
minimized the occurrence of pericarditis as a sequel to trauma, because in
their experiments it appeared to be the result of the pericardial incision.   On
the contrary, Bright and Beck [23] concluded from their experimental evidence
that hemorrhagic effusion not uncommonly developed after the myocardium
had been bruised, and Barber [17] regarded hemopericardium as "the most
important pericardial condition for consideration in connection with non-
penetrating wounds of the heart."   In any event, it is difficult to understand
by what mechanism trauma may produce, rather promptly, frankly purulent
or suppurative pericarditis, examples of which are listed in Warburg's
monograph.[8]   Sprague [24] observed tuberculous pericarditis in a Negro boxer
following a precordial blow, but correctly regarded it as an example of
"trauma and tuberculosis rather than trauma and cardiac disease."   Peri-
cardial adhesions found long after a nonpenetrating injury may or may not
be related to it.   It would seem rather arbitrary to accept a causal relation
without specific evidence of injury to adjacent structures, since similar
cardiac lesions are not uncommonly found in the absence of trauma.

Myocardial lesions following trauma may be multiple, as Moritz has

shown experimentally. Injuries caused by the steering wheel, anteriorly, may affect the posterior portion of the heart by contrecoup.[18, 23] Most frequently the contused area lies superficially, but it may be deeply situated or even isolated within the myocardium.[22] The interval which may elapse between the accident and the appearance of cardiac symptoms necessitates caution and alertness in the treatment of chest trauma.[17] Damage sustained in a previous accident may lead to subsequent rupture of the heart and sudden death. In discussing delayed rupture, Barber[17] reasons that endocardial tears are less likely to give rise to symptoms than lesions of the outer myocardium or pericardium. His personal experience and the cases collected from the literature support his inference that the essential lesion in most cases is probably a tear of the endocardium. Since many of the tears occurred with crushing chest injuries, they may be regarded as an incomplete form of the much more frequent "blow out" lesion.

Rupture of a heart valve, usually diseased, by strain or undue exertion has long been recognized.[25, 26] The aortic valve is most frequently involved, the mitral valve next. Reports of similar lesions, experimental as well as clinical, are summarized by Barber.[17] Usually such lesions lead to rapid and progressive heart failure. In an unusual case reported by Barber and Osborn,[27] the typical symptoms of mitral stenosis were observed 10 years following a traumatic lesion of the mitral valve. Barber[17] states: "There is no doubt that this healed up to mitral stenosis and the trauma was confirmed 22 years after the accident, when he died of pneumonia. There was scar tissue through the left ventricular wall, continuous into the valve." The two cases reported by Allbutt (1873),[28] which he looked upon as stenosis due to trauma, do not carry conviction, since they were not seen until about a year after the accident. Pathologically, it is difficult to explain how trauma could produce the diffuse valvular injury which would be essential to the development of stenosis.

Disturbances of rhythm following trauma may occur in the absence of demonstrable morphologic lesions.[22] Osborn[18] has found that the most common type of traumatic lesion, and one easily overlooked, is contusion of the right auricle at the entrance of the inferior vena cava, strategically close to the positions of the sinus and atrioventricular nodes. Experimentally at least, the more severe disturbances, ventricular fibrillation and immediate asystole, are more consistently associated with severe myocardial injury than are tachycardia, bradycardia or extrasystoles, and irregularity of pulse rate.[22] There may be auriculoventricular or intraventricular conduction disturbances, and many of the cases reported clinically show various abnormalities of the ST segment of the T wave. In practice, however, the diagnostic implications of such findings must be carefully evaluated in the light of any associated psychic disturbances, since it is well known that emotion or excitement, per se, are capable of producing both disturbances of rhythm and minor alterations of the electrocardiogram.[24] Consequently, the

establishment of a tenable scientific foundation requires study of cases se-
lected with the utmost conservatism, avoiding inclusion of any in which the
rôle of physical trauma may be questioned.   Only on that basis may we hope
to be able to assess accurately the clinical effects of trauma upon the heart,
despite complicating emotional factors.   Unfortunately, the very urgency
of the medico-legal situation, demanding a solution, interferes with and
prevents the proper degree of scientific detachment.   It is hardly to be ex-
pected that the physician, in his solicitude for the patient, could achieve
complete detachment, but a recognition of all possible exciting causes of
abnormality of cardiac function may lead him to adopt a more critical
attitude.

When the heart is already diseased, evaluation of the effects of trauma
is particularly difficult.   The proponents of the importance of effort and
trauma in precipitating or causing coronary occlusion [29, 30, 31] are opposed
by an equally distinguished group denying the relationship.[32, 33, 17, 24, 34]
Barber [17] and Sigler [20] support the concept that the heart in aged individuals
is more vulnerable to trauma.   Pathologically speaking, at least, it appears
equally reasonable (or incongruous) to assume that there is a greater sus-
ceptibility to a "black eye" with advancing years.   Moritz's [16] generalization
seems much more accurate and acceptable: "All persons with cardiac disease
probably pass through a stage in which the functional capacity of the heart,
although adequate to meet normal requirements, may be inadequate to re-
spond to or to recover from a strain imposed by overwork or excitement."
In reference only to traumatic heart disease of the debatable type, to insist
upon regarding trauma as more than the proverbial "last straw" is to adopt
a very broad definition of trauma which includes even the ordinary vicis-
situdes of life itself.   Such loose usage would fail to differentiate heart dis-
ease resulting specifically from contusions, lacerations, or hemorrhage into
cardiac tissue.

Sprague,[24] fully cognizant of these difficulties and pleading "for an open
mind, full experience and the rule of reason" in the evaluation of the effects
of trauma upon the heart, has set up the following criteria:

"The minimal evidence for injury to the heart *when not otherwise ex-
plained* * should be one or more of these findings: (1) significant electro-
cardiographic changes; (2) cardiac enlargement unexplained by preëxistent
cardiac disease or hypertension; (3) abnormal rhythms, not including pre-
mature beats unless supported by other electrocardiographic changes; (4)
pericardial friction rub or cardiac tamponade; (5) aortic diastolic or loud
mitral systolic murmurs with signs of congestive failure; (6) congestive
failure immediately precipitated by trauma or strain; (7) angina pectoris or
myocardial infarction starting within 24 hours of the trauma if accompanied
by distress at the time of the incident.   If the injury is severe, such condi-
tions starting at any time during convalescence can reasonably be attributed
to the traumatic event."

* Author's italics.

The accumulation and study of a significant number of cases which fulfill the desiderata established by Sprague [24] would contribute substantially to a better understanding of the subject of trauma and the heart. These are: "(1) An honest history, taken as soon as feasible after the event. (2) The absence of present or impending litigation. (3) The condition of the patient prior to trauma or strain. (4) The antecedent activities of the patient for at least a week before. (5) The customary physical and emotional habits of the subject. (6) The exact degree of injury or strain. (7) The history immediately after the episode. (8) The bridging of symptoms or "intercalary period." (9) The departure of the patient from his normal equilibrium following the episode. (10) The objective evidence of cardiac injury—change in heart size or function, pericardial or endocardial variants, electrocardiograms. (11) The assessment of the neurotic component. (12) The autopsy findings or the final recovery state."

In the following case report it was only the microscopic examination of tissues following autopsy which permitted recognition of preëxisting heart disease. All other criteria, fully as valid as those in other reported and accepted cases,[2, 4, 19, 20, 24, 26, 35, 36] "proved" it to be an example of traumatic heart disease.

A   B   C

| 1 a.m., Nov. 17 | 8 p.m., Nov. 17 | 9 a.m., Nov. 18 |
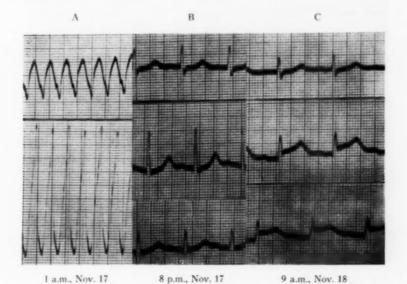
Fig. 1.   Electrocardiograms A, B, and C.   Leads I and II in A, and the three standard limb leads in B and C, showing the changes observed during the first 40 hours of hospitalization. Ventricular tachycardia in A; prolonged PR interval (0.24 second) and slightly depressed ST segment in B; in C the PR interval had increased to 0.26 second. ST is slightly depressed in Lead I and markedly elevated in Leads II and III.

CASE REPORT

A 23 year old white soldier, officer candidate, previously in good health, was ad-
mitted to a station hospital at 5:30 p.m., November 16, 1942, semi-conscious, in a state
of shock, and complaining of pain across the upper chest.   There was a history of his

D   E   F

p.m., Nov. 18   3 p.m., Nov. 19   3 p.m., Nov. 20
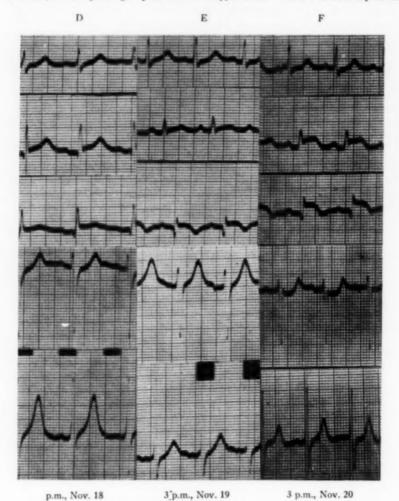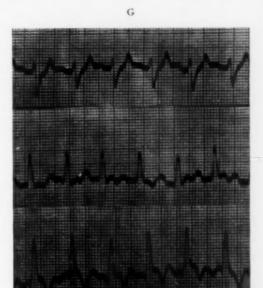
FIG. 2.   Electrocardiograms D, E, and F.   The three standard limb leads and precordial
Leads CF_2 and 4F.   Sinus rhythm with first degree A–V block continues in D, E, and F.
The ST alterations in the first three leads are of the same nature as in C of the preceding
figure.   In the precordial leads there is progressive diminution in the height of the T waves,
and of the QRS complex, to a lesser degree.   In F, CF_2 shows a depressed ST segment and
4F a final inverted phase of the T wave.

having run forcibly into a wall, striking his chest, while negotiating an obstacle course three hours previously. Although he arose, climbed the wall, and ran 50 yards to complete the course, he staggered, became pale and giddy, and suffered from a tight, painful precordial sensation. Upon admission, the arterial blood pressure measured 70 systolic and 40 diastolic, and there was very marked tachycardia of 264 a minute shown to be of the ventricular type by the electrocardiogram. Morphine, oxygen, and both digifolin (4 c.c.) and quinidine (24 gr.) were administered, but 26 hours elapsed before the heart rate and blood pressure returned to normal values. At 9:00 a.m., November 18, the arterial pressure was 110 systolic and 80 diastolic. The

G

8:15 p.m., Nov. 23

Fig. 3. Electrocardiogram G. Taken 15 minutes before death. The three standard limb leads show depression of both auriculoventricular and intraventricular conduction. Both the PR and QRS intervals are prolonged. QRS has become inverted in 1 and taller in 3. T waves are elevated in 1 and inverted in 2 and 3.

patient voided spontaneously shortly after admission, but during the subsequent seven days there was severe oliguria which resisted all therapeutic measures. Two catheterized specimens, taken on the third and sixth days, measured 250 and 370 c.c., respectively; they were highly concentrated and blood tinged (attributed to catheterization). Gallop rhythm and a pericardial friction rub were observed on the fourth hospital day. Analysis of the chemical constituents of the blood showed progressively increasing azotemia; nonprotein nitrogen attained a value of 186 mg. per hundred cubic centimeters; the figures for calcium and phosphorus were 9.7 and 8.8 mg., respectively. Death occurred on the seventh day from what appeared to be left ventricular failure.
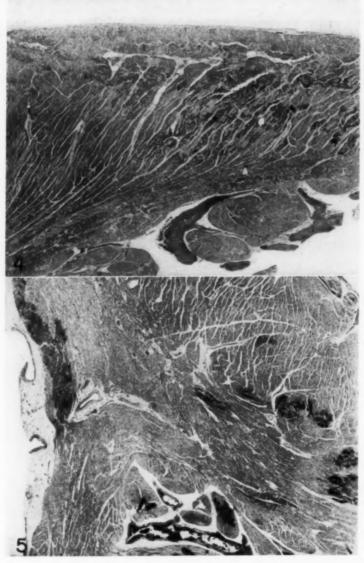
FIG. 4. Left ventricular wall. The dark staining areas, confluent beneath the epicardium, are foci of myocardial degeneration which have become calcified. Hematoxylin and eosin stain. × 10.

FIG. 5. Interventricular septum and posterior wall of heart, showing calcified foci of myocardial degeneration as in the preceding figures. Hematoxylin and eosin stain. × 10.

The electrocardiograms showing evidence of severe myocardial damage are presented in the accompanying illustrations (figures 1, 2, 3).

Autopsy performed 12 hours after death disclosed an enlarged and dilated heart; marked congestion and mild hypostatic pneumonia of edematous lungs, weighing 1,720 and 1,440 gm. on the right and left, respectively; changes in the liver and spleen interpreted as congestive; and moderately swollen and somewhat pale kidneys which weighed 210 gm. each and which exhibited accentuation of the usual architectural features. About 100 c.c. of clear yellow serous fluid had accumulated within the peritoneum; 150 c.c. of similar fluid were present in each pleural space. The thoracic cage, its clothing musculature, and the mediastinal structures showed no evidence to suggest a traumatic injury.

Since the *cardiac changes* were most striking, they will be given in detail. Grossly, marked hypertrophy and dilatation involved both the right and left sides.
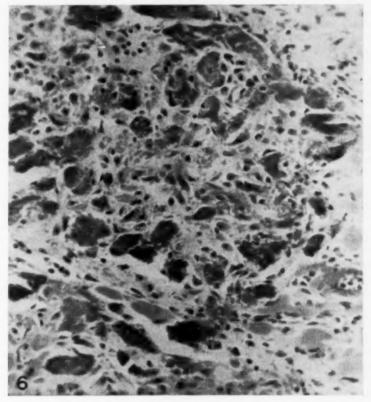
FIG. 6. The character of the myocardial degeneration and the reactive infiltration and early fibrosis, indicating the age of the lesion, are to be noted. Virtually all the muscle fibers in the field are necrotic. The irregularity of the dark stain indicates that the calcification, which accounts for it, is a secondary phenomenon. Hematoxylin and eosin stain. × 435.

The weight when emptied was 520 gm.; the right ventricle measured 8 mm., the left 20 mm. in maximum thickness. A few minor deposits of fibrin about the ostium of the superior vena cava roughened the surface of an otherwise unaltered epicardium. Both auriculoventricular rings were moderately dilated; the aortic and pulmonic rings had average dimensions. All valves were well formed, with thin, pliable leaflets, threadlike chordae tendineae, and narrow commissures. Scattered throughout the myocardium, particularly the anterior and posterior surfaces of the left ventricular wall and the interventricular septum, were firm "sandpaper-like" streaky areas of pale yellow-brown discoloration which contrasted with the reddish brown of the adjacent muscle. These areas became confluent subepicardially on the posterior wall of the left ventricle and formed a large ovoid area, 4 by 6 cm., barely discernible through the translucent epicardium. A few similar areas were observed posteriorly in the wall of the right ventricle close to the septum. In addition, the apical portions of the anterior and posterior papillary muscles of the left ventricle were yellow-gray and necrotic. A small subendocardial hemorrhage involved the region of the conduction bundle just below the membranous portion of the interventricular septum. The coronary vessels, which were thin-walled and elastic with adequate lumina throughout, had no anatomic relation to the scattered yellow areas.

Microscopic: Large scattered foci of myocardial degeneration and calcification were most prominent in the posterior wall of the left ventricle, the interventricular septum, and portions of the right ventricle and papillary muscles. The degenerated muscle fibers were swollen and intensely eosinophilic; nuclear structure and striate markings were lost. The cytoplasm was homogeneous in some areas but granular in others; in foci, the loss of occasional fibers indicated early myolysis. There was a moderate stromal reaction consisting of large mononuclear cells, fibroblasts, and a few scattered polymorphonuclear leukocytes. However, even in the midst of large areas of myocardial degeneration, the stroma was still distinctly viable. The location of necrosis did not correspond in any way to the anatomic distribution of the coronary vessels. Calcification had involved the necrotic muscle fibers and was most marked at the periphery of the larger areas of degeneration. In chosen fields, small, hyaline, cytoplasmic droplets of the degenerated muscle had assumed an intense basophilic hue indicative of calcification (verified by the von Kóssa stain). Traces of iron could also be demonstrated occasionally and inconstantly within such deposits (figures 4, 5, 6).

Other pertinent microscopic findings were: mild bronchopneumonia; marked central zonal degeneration of the liver of sufficient duration to permit removal of the necrotic cells and collapse of a stromal framework, altered only by a moderate mixed inflammatory cellular infiltrate; and typical lower nephron nephrosis.

DISCUSSION

The initiation of cardiac symptoms and the fatal course following a forcible blow to the chest in the precordial region justified the clinical impression, which was entertained, of traumatic heart disease. However, the pathologic findings—the absence of contusion and hemorrhage into the myocardium, and the lack of uniformity of the foci of necrosis, a feature described by Moritz and Atkins in experimentally induced traumatic lesions—ruled out such a diagnosis. Furthermore, the considerable enlargement of the heart, the early myolysis, and the nature of the reactive stromal response to the myocardial change found microscopically, clearly indicated a process of longer duration than the seven days of the terminal illness. The logical

conclusion is that the traumatic incident affected a heart which was already diseased, despite the apparent lack of clinical symptoms. As is well known, such a heart is particularly vulnerable to the development of arrhythmia. In this case, it seems reasonable to regard the nonpenetrating injury of the chest as the trigger mechanism which initiated the ventricular tachycardia.

The most frequent cause of major myocardial damage, myocardial infarction, may occasionally be symptomless, but the lack of relationship of foci of necrosis to the vascular tree and the normality of the coronary arteries effectively ruled out such a process in this instance. To explain the degenerative and inflammatory changes, having eliminated ischemia, one must regard the process as a form of myocarditis. Recent reviews of the subject [37, 38, 39] indicate it to be much more frequent than was previously suspected and, interestingly enough, to be often characterized by an interval free of clinical symptoms and enlargement of the heart. The lack of such a history, therefore, need not be considered of sufficient significance to rule out a process older than indicated by the clinical record. The observation of Jokl and Suzman [40] is pertinent in regard to the ability of a patient with heart disease to carry out successfully the competitive physical activity required by a military assignment: "It is remarkable that cardiovascular disease, so serious that it may cause death at any moment, does not necessarily interfere with even an extraordinarily high standard of physical efficiency."

The onset of ventricular tachycardia in a heart which anatomically could have had but little reserve resulted in a shock-like state which persisted, with the arrhythmia, for a period of 26 hours. Van Slyke [41, 42] has shown experimentally that shock prolonged for much shorter intervals produces irreversible kidney damage. While the liver is evidently less susceptible, it too is apparently vulnerable to the effects of prolonged shock.[42, 43, 44, 45, 46, 47] At any rate, from what is known regarding the sequential changes in central zonal necrosis of the liver [48] and lower nephron nephrosis,[49] both lesions appeared to be of the same age and were compatible with an onset at or shortly after the initiating trauma. Other factors which might have explained these two lesions were not present. It seems likely that each of them exerted a perpetuating and augmenting effect on the other, a process well established clinically as the hepatorenal syndrome. Excretion of degradation products of hemoglobin, myoglobin, or other protein materials (as in burns) has been recognized as etiologically significant in the pathogenesis of lower nephron nephrosis.[50] In this instance, it was readily apparent that circulating products of liver cell disintegration served to accentuate the renal damage sustained as a result of prolonged shock. In turn, the mounting azotemia of renal insufficiency could scarcely provide the proper milieu for the survival or resuscitation of severely injured liver cells. The accumulations of fluid in abdomen and thorax, the pulmonary edema, and the congestive changes were consequences of the heart and kidney lesions. The slight fibrinous deposit on the pericardium was probably attributable to

uremia. The curious deposition of calcium upon the necrotic muscle fibers is considered at length elsewhere,[51] but, in brief, was a consequence of changes in the balance of calcium and phosphorus produced by renal failure.

SUMMARY

Lesions of the heart produced by nonpenetrating trauma (specifically, only injuries which do not cause death promptly) are not fully understood, because most of the literature regarding heart disease of this type is based entirely upon clinical evidence. Furthermore, the autopsy evidence, cited in a minority of cases, has been accepted uncritically.

A case from the Armed Forces Institute of Pathology illustrates the unreliability of the diagnosis of traumatic heart disease arrived at from clinical evidence alone. Autopsy disclosed that heart disease had preceded the traumatic episode, which acted as the trigger mechanism to precipitate the terminal illness.

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STREPTOCOCCIC VIRIDANS MENINGITIS: A REVIEW OF THE LITERATURE AND REPORT OF NINE RECOVERIES *

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Insofar as we were able to determine, a complete review of the literature on *Streptococcic viridans* meningitis has never been published. Gray [19] reported that, for the period 1901 to 1935, he was able to gather only 66 cases of recovery from streptococcic meningitis of all types. But two years later, in 1937, Trachsler et al.[63] added 44 cases, five of which were their own. Of these 110, only five of Gray's were due to *Streptococcus viridans,* and Trachsler et al. had but four. Thus a total of only nine recoveries from *Streptococcic viridans* meningitis seems to have been reported before 1937, when the sulfonamides were announced. Since 1937 there has been an increase in the number of patients with *Streptococcic viridans* meningitis in whom the outcome has been favorable. However, including the nine mentioned above, there appear to have been but 25 recoveries, and consequently, our additional nine make a total of 34 who have survived attacks of this form of meningitis.

In view of the foregoing, it occurred to us that a review of the literature in respect to *Streptococcic viridans* meningitis should be made because of the exceptional interest now displayed in all forms of meningitis. Moreover, it is our purpose to discuss certain facts relating to this form of meningitis which were not always alluded to in previous reports. Factors deserving the utmost consideration are necessarily the etiology in relation to diagnosis and also the possibilities of response to appropriate treatment.

We have reviewed the reports of nine patients who recovered prior to 1937. Also, we have been diligent in our efforts to find every reported recovery or death following *Streptococcic viridans* meningitis since 1937. In particular, we have searched the files of Cook County Contagious Disease Hospital (1943 to 1948) and Chicago Municipal Contagious Disease Hospital (1938 to 1948) for deaths or recovery from the disease. The cases found are discussed in this article and represented in table 1. Records of the past few years from the general wards of Cook County Hospital disclosed two more recoveries and four deaths. These are included also in table 1 as Cases 35 and 36, and in table 2 as Cases 30, 31, 32, and 33. However, we have excluded cases listed in hospital records as *Streptococcic viridans* meningitis when we found from a study of the patient's chart that laboratory

TABLE I

Reported Recoveries—*Streptococcus viridans* Meningitis

Case No.		Year	Age	Sex	Probable Source of Infection	Spinal		Blood Cult.	Treatment	Condition on Admission	No. Days in Hospital Course	Remarks
						Culture	Cell Count					
1	McCarthy[20]	1916	25	M	Head injury	+	NR	NR	Daily punctures. Human serum IT.	Delirious	10	
2	Weaver[27]	1918	23	F	None found	+	2,750	NR	Antimeningococcic serum 7X IT. Antistreptococcic serum 4X IT and IM.	Rigid neck vomiting	31—Stormy	
3	Pateig[28]	1921	18	M	None found	+	Cloudy	NR	Conservative therapy; 1 lumbar puncture.	Rigid neck	22	
4	Dandy[29]	1924	49	F	Surgery for cerebellar tumor	+	1,840	NR	Daily L.P. 35 days; continuous. Cisternal drainage 4 days.	Febrile rise 8 to 15 days post-op.	43—Stormy	
5	Ebert[13]	1930	15	M	Rhinitis-maxillary sinusitis	+	Turbid	NR	Antimeningococcic serum. Maxillary sinus antrotomy.	Rigid neck	10	
6	Felsen and Osofsky[14]	1934	22	M	Scalp laceration	+	5,000	NR	Gas gangrene serum 4X IT.	Drowsy; headache	10	
7	Zeligs[71]	1935	11	M	None found	+	6,700	NR	Continuous spinal drainage. Injection of air for block.	Convulsions Semi-comatose	23	Congenital pulmonic stenosis.
8	Tripole[69]	1936	12	F	Otitis media	+	NR	-	Mastoidectomy. Repeated lumbar taps. Antimening. serum in cistern.	Meningeal signs	20	
9	Williams and Simonton[59]	1936	13	F	Petrositis	+	3,200	NR	Mastoidectomy. Continuous spinal drainage.	Rigid neck vomiting	30	
10	Appelbaum[1]	1938	NR	NR	Chronic sinusitis	+	NR	NR	Sulfanilamide. Spinal drainage.	Comatose	NR	
11	Sappington et al.[51]	1939	5	M	None found	+	570	NR	Sulfanilamide 0.6 gm. q. 4 H. also given IT.	Rigid neck	11	
12	Greengard, Raycraft, et al.[30]	1940	11 days	F	Omphalitis	+	Very many	+	Sulfapyridine 0.25 gm. q. 4 h.	Drowsy Toxic	72	
13	Mitchell et al.[39]	1940	54	M	Nephrolithiasis	+	8,500	NR	Sulfapyridine 2 gm. q. 4 h.	Convulsions Opisthotonos	NR—Rapid	
14	Mitchell et al.[39]	1940	1½	M	Otitis media	+	1,900	NR	Sulfapyridine 1.0 gm. q. 4 h. myringotomy.	Stuporous, convulsions	NR—Rapid	
15	Mitchell et al.[39]	1940	8	M	None found	+	1,800	+	Sulfanilamide. Sulfapyridine. X-ray to base of skull.	Rigid neck	NR—Slow	Rapid improvement after x-ray therapy.

TABLE 1—*Continued*

Case No.		Year	Age	Sex	Probable Source of Infection	Spinal		Blood Cult.	Treatment	Condition on Admission	No. Days in Hospital Course	Remarks
						Culture	Cell Count					
16	Blumberg and Zisserman[6]	1941	42	M	None found	+	2,800	−	Sulfapyridine 2–3 gm. q. 4 h.	Headache	26	Temporary uremia.
17	Cameron[12]	1941	9	M	Maxillary sinusitis	+	Turbid	NR	Soluseptasine 1.0 gm. q. 4 h. Sinus antrotomies.	Semi-conscious Restless	18	Cultures of sinuses positive for *Streptococcus viridans*.
18	Rantz[54]	1942	65	F	Frontal and maxillary sinusitis	+	2,400	NR	Sulfanilamide—2 days. Sulfapyridine 1.0 gm. q. 4 h.	Stuporous	49	No effect after 20 gm. sulfanilamide. . Marked improv. after sulfapyridine.
19	Fleming[?]	1943	52	M	None found	+	500	NR	Sulfapyridine 1.0 gm. q. 4 h. 1st wk. Sulfathiazole 1.0 gm. 2nd, 3d wk. Penicillin 5–10,000 U. q. 2 h. I.M. 5,000 U. IT 5 times.	Semi-delirious Drowsy	56—Stormy. Immed.improv. with penicillin	Organisms found resistant to sulfathiazole, sensitive to penicillin. Relapse on penicillin but rapid recovery after IT penicillin.
20	Rosenberg and Arling[56]	1944	18	M	None found	+	450	+	Penicillin 10,000 U.q. 2 h., 4 days; 10,000 U. IT 4 times.	Comatose	NR—Rapid recov. only 4 days Rx	Naval personnel.
21	Wollgast[70]	1944	NR	NR	Head injury	+	Many	NR	Sulfadiazine—then penicillin IM and IT.	NR	11—Stormy	No response to sulfadiazine. Response to penicillin only after IT air injections.
22	Brockway and Jacobs[?]	1945	9	F	Dental alveolar abscess. Pos. culture	+	1,000	+	Sulfadiazine 1.0 gm. q. 4 h. Penicillin 10,000 U. q. 3 h. after the 6th day 20,000 U. IT, 8 times.	Lethargic	15—Stormy	Rapid improvement only after use of penicillin also, though organisms equally sensitive to both drugs.
23	Cardelle et al.[13]	1945	45 days	F	None found	+	31,000	NR	Sulfamerazine 0.5 gm. q. 8 h. 23 days. Penicillin 5,000 U. IM q. 3h. 23 days. Penicillin 10,000 U. IT 6X; in cistern 1X.	Stuporous Convulsions	NR—Fairly rapid	Moderate hydrocephalus resulted.
24	Kyes[?]	1947	60	M	Pneumonia	+	1,000	+	Sulfadiazine 7 days. Penicillin 20–50,000 q. 3 h. IM—IT once.	Comatose	32	
25	Livingstone and Leach[?]	1947	59	F	Excision of nasal tumor	+	Clear	NR	Sulfadiazine 1.0 gm. q. 4 h. Penicillin 80,000 q. 3 h.; 5X IT.	Febrile rise	38—Convulsions associated with IT therapy	IT penicillin started after spinal cultures neg. Authors believe IT therapy responsible for recovery.

TABLE I—*Continued*

Case No.		Year	Age	Sex	Probable Source of Infection	Spinal		Blood Cult.	Treatment	Condition on Admission	No. Days in Hospital Course	Remarks
						Culture	Cell Count					
26	Case 1	1944	6	F	None found	+	1,300	–	Sulfathiazole 1.0 gm. q. 4 h. 1 wk. Sulfadiazine 0.75 gm. q. 4 h. 2nd wk.	Stupor Hemiplegia	Fairly rapid recovery	Rheumatic heart disease, but 16 negative blood cultures.
27	Case 2	1945	29	F	None found	+	400	–	Sulfathiazole 2.0 gm. q. 4 h.	Comatose Restless	16	Complication of post-meningitis psychoses—cure of meningitis.
28	Case 3	Jan. 1946	33	M	Suppurative otitis media	+	15,000	+	Sulfathiazole 2.0 gm. q. 4 h. Penicillin 30,000 U. q. 3 h.; 40,000 IT 1X.	Semi-rational Restless	12	Paresis of right and left lateral recti upon recovery.
29	Case 4	Jan. 1946	45	F	Suppurative otitis media	+	16,800	–	Sulfathiazole 2.0 gm. q. 4 h. Penicillin 30,000 q. 3 h.; 40,000 IT 2X.	Delirious Restless	14	Transient diplopia.
30	Case 5	1947	11 mos.	F	None found	+	460	–	Sulfathiazole 0.5 gm. q. 4 h. Penicillin 20,000 U. q. 3 h.	Depressed sensorium	16	
31	Case 6	1938	9	F	Suppurative otitis media	+	10,000	–	Sulfanilamide 1.0 gm. q. 4 h. Myringotomy.	Semi-delirious	19—Stormy	
32	Case 7	1944	7	M	Suppurative otitis media	+	325	NR	Sulfadiazine 0.5 gm. q. 4 h.	Restless Irritable	22	
33	Case 8	1945	5 mos.	M	Draining sinus base of spine	+	960	–	Sulfadiazine 0.5 gm. q. 4 h. Penicillin 10,000 U. q. 2 h. 10,000 U. IT 1X.	Stiff neck	56—Recovery from meningitis	Transferred for surgery of epidural abscess.
34	Case 9	1947	6 mos.	M	None found	+	630	–	Sulfadiazine 0.5 gm. q. 4 h. Penicillin 30-100,000 U. q. 3 h. Sulfathiazole 0.5 gm. q. 4 h. Streptomycin 0.1 gm. q. 3 h. 1 wk.	Lethargic	44—Stormy	Cure apparently only after use of massive doses of penicillin. Streptomycin had no apparent effect.
35	A. D. Cook County Hosp.	Jan. 1946	12	M	None found	+	6,400	NR	Sulfadiazine 1.0 gm. q. 4 h. Penicillin 20,000 U. q. 3 h. Penicillin 20,000 U. IT once.	Headache Vomiting Stiff neck	15	
36	H. T. Cook County Hosp.	Feb. 1946	49	F	None found	+	10,000	–	Sulfadiazine 1-2 gm. q. 4 h. Penicillin 40,000 U. q. 3 h. Penicillin 40,000 U. IT 8X.	Stuporous	39—Stormy	Sensorium remained much depressed even after spinal cultures negative. But IT penicillin given on six additional occasions.

TABLE II

Reported Deaths Following *Streptococcic viridans* Meningitis

Case No.	Author	Year	Age	Sex	Probable Source of Infection	Cult. S. Fl	Treatment	Remarks
1-2	Tripoli[58]	1936	NR*	NR	NR	NR	NR	
3	Neal et al.[42]	1936	13	M	Subacute bact. endocard.	+	NR	Clinical diagnosis
4	Neal et al.[42]	1936	25	M	Subacute bact. endocard.	+	NR	subacute bact.
5	Neal et al.[42]	1936	67	F	Subacute bact. endocard.	+	NR	endocarditis
6	Neal et al.[42]	1936	44	F	Subacute bact. endocard.	+	NR	
7	Trachsler et al.[68]	1937	12	M	Basal skull fracture	NR	Prontosil	Reported as viridans meningitis
8	Appelbaum[2]	1938	NR	NR	ENT infection	+	Sulfanilamide	
9	Smith[53]	1939	NR	NR	Subacute bact. endocard.	+	Sulfanilamide	†
10	Roch and Neeser[46]	1939	43	M	Subacute bact. endocard.	+	Sulfanilamide	‡
11	Noble[44]	1939	NR	NR	Mastoiditis	+	Sulfanilamide	No response to therapy
12	Sappington[57]	1939	59	M	Otitis media	+	Sulfanilamide	36 hour death
13, 14, 15	Mitchell et al.[19]	1940	NR	NR	Not reported	NR	Sulfanilamide	Reported only as 3 cases viridans men.
16	Rantz[52]	1940	52	M	Purulent parotitis	+	Sulfanilamide	
17-25	Hertzog[26]	1945	NR	NR	Many due to ENT infection	+		9 cases—autopsy records in 10 yrs. Univ. of Minn.
26	Kornblum et al.[31]	1947	1½	M	None found	+	Chemotherapy	
27	Case Report 10	1947	43	M	Otitis media	+	Sulfathiazole	27 hour death
28	Case Report 11	1946	48	F	None found	+	Sulfadiazine	
29	Case Report 12	1944	51	M	Subacute bact. endocard.	+	Sulfathiazole	Autopsy
30	B. C., Cook County Hospital	Feb. 1946	65	F	None found	+	Penicillin 100,000 U. stat 20,000 U. q 3 h.	Admitted in coma 14 hour death
31	M. C., Cook County Hospital	Jan. 1946	80	F	None found	+	Sulfathiazole 5 gm. IV	Admitted in coma 5 hour death
32	C. K., Cook County Hospital	Jan. 1946	65	M	Pneumonia	+	Sulfathiazole 10 gm. IV	Admitted in coma 11 hour death
33	N. W., Cook County Hospital	Jan. 1946	40	M	Rhinitis	+	Sulfadiazine 2.5 gm. stat IV Penicillin 40,000 U. IT 20,000 U. q 3 h	Admitted in coma with convulsions 5 hour death

* No report—NR.
† Meningitis recovery; patient died 2 months later from subacute bacterial meningitis.
‡ Meningitis recovery; patient died 4 months later from subacute bacterial endocarditis.

data were incomplete or that the diagnosis was inconclusive for other reasons. There were four such instances.

Incidence. It is an established fact that *Streptococcus viridans* is an infrequent invader of the meninges and that recovery from this kind of meningitis is rare. There is little in the nature of true statistical reporting of this type of disease because, in the largest surveys of meningitis, it has been the custom to include this infection under the general category of streptococci. Furthermore, bacteriologic diagnosis in reported cases of strepto-

coccic meningitis frequently consists of merely designating the organism as a streptococcus, without further classification of its species and with failure to report the nature of the hemolysis on blood agar.

The uncommon incidence is well illustrated by our present study, in which the entire literature to 1948 has disclosed only 25 recoveries. However, 26 deaths have been recorded since 1937, making a total of 51 known cases of viridans meningitis.

Neal, in 1924,[40] listing 83 cases of streptococcic meningitis in her extensive series, says that "practically all the cases (of streptococcic meningitis) are due to one of the hemolysing streptococci" and that *"Streptococcus viridans* rarely causes meningitis." The available statistical figures are presented in table 3 and indicate that *Streptococcic viridans* meningitis generally occurs in an incidence of 0.3 per cent to 2.4 per cent of all types of purulent meningitis.

In the largest series of bacterial meningitis observed in the literature, that by Neal in 1938,[41] there is an analysis of 3,502 cases, with the disclosure that streptococci were the etiologic agent in 274 (12.5 per cent). Table 3 indicates a general decline in this incidence of streptococcic meningitis, for it is seen that there has been at Cook County Contagious Hospital for the

TABLE III

Incidence of *Streptococcic viridans* Meningitis

Author or Source	Cases Bacterial Meningitis	Cases Streptococcic	Per Cent Streptococcic	No. Viridans	Per Cent[*] Viridans	Per Cent[†] Viridans
Neal[40]	—	83	—	rare	—	—
Recoveries[19,63] in literature until 1937	—	110	—	9	8.1%	—
Tripoli[66]	468	24	5.1%	3	12.0%	0.6%
Neal[41]	3,502	274	12.5%	—	—	—
Cook County[63] Contagious Hospital[‡]	459	42	9.0%	6	14.0%	1.1%
Rantz[60]	36	6	16.0%	1	17.0%	2.8%
Hartmann et al.[33]	100	12	12.0%	—	—	—
Hertzog[24][§]	377	54	14.0%	9	17.0%	2.4%
Cook County Contagious Hosp. 1943 to 1947, inc.	1,099	12	1.1%	8	67.0%	0.7%
Municipal Contagious Hosp. 1938 to 1947, inc.	1,325	38	3.0%	4	10.0%	0.3%

* The percentage of cases of *Streptococcic viridans* meningitis to the total number of cases of all types of streptococcic meningitis.
† The percentage of cases of *Streptococcic viridans* meningitis to the total number of cases of all types of bacterial meningitis.
‡ Chicago. Includes years 1937 to 1939, inclusive.
§ Includes only the necropsy cases at the University of Minnesota, 1935 to 1944, inclusive.

TABLE IV

Probable Port of Entry in *Streptococcic viridans* Meningitis

Port of Entry	Recoveries		Deaths		Total Cases		Per Cent Recoveries for Each Port of Entry
	No.	Per Cent	No.	Per Cent	No.	Per Cent	
None found	15	42.0	4	16.0	19	35.0	80.0
Ear and nose	12*	33.0	5†	25.0	17	31.0	70.0
Subacute bacterial endocarditis	0	0	7	35.0	7	13.0	0
Totals	36‡		19§		55		

* Includes one case of nasal surgery.
† This does not include the fatal cases (9) of Hertzog in which the focus of infection in the majority was probably in the nose and ear.
‡ Includes recoveries in one case each of pneumonia, nephrolithiasis, omphalitis, epidural abscess, dental alveolar abscess, scalp laceration, cerebellar tumor surgery, possible fracture cribriform plate, and head injury.
§ Includes deaths in one case each of parotitis and pneumonia.

years 1937 to 1940 an incidence of 9.0 per cent,[53] while we report but 1.1 per cent for the five-year period 1943 to 1948. Likewise, for the decade 1938 to 1948, at Chicago Municipal Contagious Disease Hospital, there has been an incidence of 3 per cent for streptococcic meningitis. Apparently, similar observations were made by White [68] in 1945, for he observed that "due to the effectiveness of sulfonamides in acute streptococcal infections, and especially those infections involving the rigid, pneumatic chambers of the head, such as mastoiditis and sinusitis, the incidence of streptococcic meningitis has been markedly reduced."

That there may be an increase in the percentage of *Streptococcic viridans* meningitis as related to total streptococcic meningitis is evident from table 3, where it is shown that at Cook County Contagious Hospital the proportion of viridans meningitis to other streptococcic meningitis was 14 per cent [53] from 1937 to 1940, while in the period 1943 to 1948 it was 67 per cent. Perhaps an explanation may be evident in table 4, where we show that only 31 per cent of cases of viridans meningitis followed ear, nose and throat infections, whereas in 70 per cent [42] of hemolytic streptococcic meningitis there was a previous ear, nose and throat infection to explain the pathogenesis. Also because of White's observation [68] that streptococcic meningitis is decreasing due to fewer severe ear, nose and throat infections, we may conclude that *Streptococcic viridans* meningitis will hereafter assume increasing importance among the streptococcic meningitis group.

In general, the incidence of *Streptococcic viridans* meningitis is low. But because we were able to find four cases (1938 to 1948) at Municipal Contagious Disease Hospital and eight cases (1943 to 1948) at Cook County Contagious Disease Hospital, it seems likely that a fair portion of this type of meningitis has not been reported.

In table 1 we have summarized the 25 reported recoveries. In table 2 we have listed 26 deaths found in the literature since 1937. In each of these tables also will be found the cases we ourselves have investigated.

Etiology. Bacteriology: The *Streptococcus viridans* is considered by most bacteriologists to be a *group* of organisms among the genus streptococcus, and not a specific organism. Among this "viridans group" there are the following main types[62]: *Str. salivarus,* occurring in the human mouth and intestine; *Str. mitis,* in the human mouth; *Str. equinus,* in the intestines of the horse; *Str. bovis,* in the intestines of the cow; and, finally, *Str. acidominimus,* found in the milk, feces, and vagina of cows. Recently, *Streptococcus s.b.e.* has been described; it seems to occur chiefly in penicillin treated patients suffering from subacute bacterial endocarditis.

TABLE V

Age Incidence *Streptococcic viridans* Meningitis

Age Group	Recoveries	Deaths	Total
Under 1 year	5	0	5
1 to 5 years	1	1	2
5 to 10 years	8	0	8
10 to 18 years	4	2	6
18 years and over	16	13	29

In the laboratory, practical differentiation of this viridans group of streptococci from all other streptococci is made on the basis of the nature of the hemolysis when the organisms are grown on blood agar. On the strength of this hemolysis, streptococci can be differentiated[62, 9] into three types: A (alpha) hemolytic or viridans (green) streptococci, B (beta) hemolytic streptococci, and G (gamma) non-hemolytic or "indifferent" streptococci. There are other gram-positive coccus organisms, chiefly the pneumococcus, which produce alpha hemolysis, and differentiation from the pneumococcus is important clinically. This differentiation is made upon the following criteria[62, 3]: The pneumococcus in the presence of type specific anti-serum will produce the Neufeld "quellung" phenomena; *Streptococcus viridans* will not. *Streptococcus viridans* is not bile-soluble, and seldom ferments inulin, whereas the pneumococcus is bile-soluble and ferments inulin.

Age: The age incidence of all cases in this article is presented in table 5, where it appears that this disease attacks adults more frequently than children. However, the youngest recovery was that of an eleven-day-old baby girl, reported by Greengard, Raycraft, et al.[20]; the eldest was a 65 year old woman reported by Rantz.[52]

Sex: There was a total of 29 males and 20 females, of whom 19 males and 14 females recovered.

Port of Entry: Although much has been written [42, 24, 23, 19, 71] about the probable source of infection in hemolytic streptococcic meningitis, little has been said concerning the port of entry in *Streptococcic viridans* meningitis. Usually great emphasis is placed on the ear, nose and throat as a focus for *Streptococcic hemolyticus* meningitis.[42, 24, 23, 19, 71]

The viridans group of streptococci are common inhabitants of the respiratory tract of both diseased and normal individuals, where they predominate or may even be the sole organism.[58, 5, 62, 49] Because of low virulence, they have never been known to be the cause of sore throats, but apparently exist in throats in a saprophytic capacity.[5, 49] They may be isolated frequently in localized septic lesions in connection with the teeth and gums [21, 54, 45, 47, 3] and in infections of the nasal sinuses [3, 5] and the middle ear.[3, 5] Other nonrespiratory sources [5] include the genito-urinary tract and bladder, and the large intestines; and, finally, the *Streptococcus viridans* is the most frequent organism isolated from the blood in individuals with subacute bacterial endocarditis.[3, 5, 62] Each of these areas of focal infection has been credited by authors with having been the probable source of infection in cases of *Streptococcic viridans* meningitis. How the organism reaches the meninges from these primary sources is not definitely known, and is probably impossible to prove. Whether by contiguity of structure, as in the nasal sinuses and middle ear, or by bacteremia from teeth,[45, 47, 21] gums,[54] tonsils,[54] genito-urinary tract,[39] or valvular endocarditis,[59] can rarely be determined.

Due to the paucity of the literature on viridans meningitis and the absence of a previous review of the subject, accurate figures on sources of infection are lacking. Nevertheless, it has been stated [48, 8, 32] that viridans meningitis rarely occurs without a concomitant subacute bacterial endocarditis. But in our analysis we find (table 4) that of the 55 cases, there was an ear, nose, or throat source in 31 per cent, and that the meningitis followed a subacute bacterial endocarditis in only 13 per cent. In 35 per cent no primary focus of infection was disclosed. Furthermore, it is apparent from the literature that the occurrence of *Streptococcic viridans* meningitis secondary to subacute bacterial endocarditis is in itself not common. Tice [61] remarks that "in a few instances (of subacute bacterial endocarditis) the *Streptococcus viridans* has been cultured from the spinal fluid." Many others in authoritative writings do not even refer to meningitis as a possible complication of subacute bacterial endocarditis.[59] Smith,[59] reviewing the literature up to 1939, found only five instances with positive spinal fluid cultures for *Streptococcus viridans* complicating subacute bacterial endocarditis. However, there was a total of 30 cases with clinical evidence of meningitis complicating subacute bacterial endocarditis. Neurologic signs apparently were such that Neal et al.[43] were able to gather 41 cases seen in consultation because of symptoms suggestive of meningitis, encephalitis, or poliomyelitis.

In reality, these patients had embolic manifestations of an underlying and frequently unsuspected subacute bacterial endocarditis. But only four of these 41 patients had positive spinal fluid cultures. Smith[59] concludes that true bacterial meningitis is an "unusual" manifestation of subacute bacterial endocarditis; however, in a case of *Streptococcic viridans* meningitis, subacute bacterial endocarditis must enter into the differential diagnosis. Smith expressed the opinion that meningitis due to *Streptococcus viridans* when occurring as a complication of endocarditis is of a benign nature and usually is of short duration, subsiding spontaneously. Our own experience and that of others[8] has not been in accord with such views.

CLINICAL OBSERVATIONS

There are no characteristic features in regard either to onset or later symptoms which are suggestive of the etiologic factor in this form of meningitis. Although the illness in most of our nine recovered patients began with a convulsion in infants, or a chill in those who were older, and vomiting occurred during the attack, these disturbances alone are not distinctive for meningitis. Moreover, it should be remembered that infants may have meningitis without neurologic signs. This last named fact emphasizes the importance of lumbar puncture in cases of doubtful diagnosis, even though there may be no nuchal rigidity.

The ages among our group of recoveries ranged from five months to 45 years for the five female and four male patients. The high cell counts in the spinal fluids as a rule approached 90 per cent polymorphonuclears. In two instances, smears were reported negative for organisms, but cultures of *Streptococcus viridans* from the spinal fluid were positive for all. Only two of the nine patients had positive blood cultures. All were treated with a sulfonamide, and sulfathiazole was the drug of choice for seven. Penicillin was also administered to six patients. Only three of those who recovered received any intrathecal therapy.

PROGNOSIS

Condition on Admission: Analysis of the recoveries discloses that there was a total of 18 admitted in coma or in delirium, with or without convulsions, and also 17 admitted with signs only of meningeal irritation. However, of the nine recoveries prior to sulfonamides, only two were comatose or delirious on admission, while of the 26 recoveries since sulfonamides there were 16 patients comatose or delirious on admission.

It is of interest to note that of the 12 cases we are reporting, and the additional two cases in table 1 (Cases 35 and 36), and the four in table 2 (Cases 30, 31, 32 and 33), or a total of 18 from the Chicago area, there were 10 patients who were hospitalized during January and February, 1946. Of these 10, eight cases were admitted comatose or delirious, and six of these died. Five of the deaths were within approximately 24 hours of admission,

two in five hours, and one each in 11 hours, 14 hours, and 27 hours. The age range in this group of fatalities was 40 to 80 years. No epidemiologic explanation is available to fit these facts.

Hospital Course: Among the surviving patients, approximately one-half made "rapid recoveries," that is, were fully conscious and afebrile after one week of therapy and remained so. Others made slow progress, while the courses of some were very stormy. The rate of improvement appeared to bear no relationship to the form of therapy.

Age: On the basis of our study, the prognosis seems to be more favorable for those under 18 years of age than for those who are older. Whether this is actually true is uncertain, because while all recoveries are likely to be reported, it is probable that all deaths are not.

Port of Entry: Although no marked difference is evident from our figures to suggest that the port of entry is a significant influence in prognosis, we believe that the outcome is less favorable when the meningitis is known to follow nasal and aural infections.

TREATMENT

Poston and Orgain [50] have reported on the in vitro effect of sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine against 25 strains of *Streptococcus viridans* isolated from blood of patients with subacute bacterial endocarditis. They concluded that sulfapyridine, which was completely effective against 13 strains, was the drug of choice. Eight strains were found against which none of the sulfonamides tested was effective. However, there was no strain inhibited by any sulfonamide against which sulfapyridine was not equally effective. From the report, we conclude that the other sulfonamides tested were of value in the following order of decreasing effectiveness: sulfathiazole, sulfadiazine, and sulfanilamide. Other writers,[64, 22, 60, 7, 5, 46] in smaller series of tests, found wide variations in the in vitro effect of sulfonamides on *Streptococcus viridans,* with some strains being completely non-sensitive to all sulfonamides tested, or varying widely in their sensitivity to the same drug. As to the individual sulfonamides, not enough complete and extensive studies appear to have been made [50] to warrant any conclusions on our part as to which is most effective against *Streptococcus viridans.*

Milzer,[38] in testing 31 strains of *Streptococcus viridans* isolated from throats of rheumatic fever patients, demonstrated that most of the organisms were sensitive to penicillin in concentrations of 0.15 U./c.c. to 0.31 U./c.c. Three organisms were resistant. Dawson and Hobby [14] tested 19 strains of *Streptococcus viridans* isolated from patients with subacute bacterial endocarditis. They found one resistant strain, and found that most strains were two to four times less sensitive to penicillin than was a standard strain of beta hemolytic streptococcus. Meads [37] tested 24 strains isolated from a variety of sources, and likewise observed them to be two to four times less sensitive than the beta hemolytic streptococcus control. On the basis of

similar experiments, writers [37, 62] agree that the *Streptococcus viridans* compares in its penicillin sensitivity range to that of the pneumococcus, but is more resistant than *Streptococcus pyogenes*. We must therefore conclude, in consideration of these reports,[14, 38, 17, 37] that although *Streptococcus viridans* is generally sensitive to penicillin, and more so than to the sulfonamides, there is a wide variation in this sensitivity, and that about 10 per cent of the strains are resistant to penicillin.

Finally, in this discussion of sensitivity, there arises the question of a synergism between the sulfonamides and penicillin in their activity against *Streptococcus viridans*. While most writers on the subject report the existence of this synergism,[35, 66] Hobby and Dawson do not concur.[25] Massell et al.,[35] in studying the problem, found that the minimal effective concentration of penicillin is considerably reduced in the presence of sulfonamides, though with penicillin in amounts above the minimal effective concentration, sulfonamides do not appreciably alter the bactericidal action of the penicillin. In addition, they encountered some strains of viridans for which a synergism could not be demonstrated.

Thus far, streptomycin has not been used on a scale sufficiently extensive to judge its true value. However, its effectiveness has been determined for some strains.[51, 30]

TREATMENT OF STREPTOCOCCIC VIRIDANS MENINGITIS

On the basis of their own observations, or on the limited experience of others, some authors have ventured guarded opinions on therapy, especially in respect to sulfanilamide. Anderson [1] concluded that, while sulfanilamide was quite effective against hemolytic streptococcic meningitis, it had no value against meningitis due to other strains of streptococci. A report of the American Medical Association Council on Pharmacy and Chemistry [12] in 1937 stresses that sulfanilamide had not been successful against infections due to alpha hemolytic (viridans) streptococci. Unsuccessful results with sulfanilamide have been reported in the treatment of seven patients suffering from *Streptococcus viridans* meningitis: three by Mitchell et al.[39] and one each by the following: Appelbaum, Sappington and Favorite,[57] Rantz,[52] and Noble.[44] However, in spite of these failures this drug apparently has some worth, as indicated by reports of three recoveries in which sulfanilamide alone was used: one case each of Sappington and Favorite,[57] Appelbaum,[2] and Case 6 in our case reports. We might surmise from these data that in the failures the strains were resistant to the action of sulfanilamide, while in the recoveries the organisms were sensitive to the same drug.

There are a few instances reported, also, where one drug was ineffective while another proved successful. Rantz [52] found marked improvement in his patient on change to sulfapyridine, after unsuccessful use of sulfanilamide. Fleming's [18] case proved to be one in which the organism was resistant to sulfathiazole but sensitive to penicillin, and there was immediate improve-

ment after penicillin therapy was instituted. A case is reported by Brockway and Jacobs [8] in which there was rapid improvement after the addition of penicillin to the sulfadiazine regime in use, although in vitro studies disclosed that the organism was equally sensitive to both penicillin and sulfadiazine. We found in Case 9 that a cure was effected only after massive doses of penicillin (100,000 units every three hours) were given.

From a study of "Treatment" in tables 1 and 2, it may be seen that no accurate conclusions regarding the choice of drug or drugs can be drawn. We find recoveries have been effected with sulfonamides and penicillin, singly and in all manner of combinations and dosage. Moreover, it is probable that not all the deaths were found by our review, and possibly some recoveries do not appear in the literature. Nevertheless, there have been 13 recoveries (87 per cent) out of a total of 15 cases in which penicillin was used in conjunction with a sulfonamide, while there were only 13 survivals (50 per cent) among 27 patients in whom a sulfonamide was used alone. Such results suggest that penicillin is a definite aid in treatment. But that this effect is due to synergism is unlikely, as Massell [35] demonstrated in vitro that if penicillin is present in a concentration well above that of the sensitivity of the strain of viridans streptococcus being tested, sulfonamides will not alter appreciably the rate at which the organisms are killed. Perhaps a better explanation would be that probably many more strains of *Streptococcus viridans* are sensitive to penicillin than to the sulfonamides.

It must still be remembered, however, that about 10 per cent of the strains are resistant to penicillin. Though there has not been a study of this nature, it is felt that some, if not all, of these penicillin-resistant strains, may be sensitive to sulfonamides. As to the choice of the sulfonamide, thus far no final conclusions are warranted. However, in our review there were seven deaths and three recoveries in which sulfanilamide was used, whereas with sulfapyridine therapy there were six instances without a fatality. Other sulfonamides were not used alone extensively enough to justify conclusions as to their efficiency. However, we found among the 13 recoveries in which both penicillin and a sulfonamide were employed that seven received sulfadiazine.

That penicillin need not be given intrathecally was demonstrated by two recoveries where the intramuscular route alone was adopted for this drug. Both these patients were treated also with a sulfonamide. In four other recoveries only one dose of penicillin was given intrathecally. Several series of meningococcic meningitis [26, 27, 29] and influenzal meningitis [28] without intrathecal therapy and with few lumbar punctures have been reported by one of us.

From the foregoing discussion certain conclusions may be drawn. Strains of *Streptococcus viridans* vary considerably in their degree of sensitivity to different sulfonamides and to penicillin. Some strains are resistant to either sulfonamide or to penicillin. Successful treatment may

depend on the use of sensitivity tests against the offending organism. When the organism is obtained from the spinal fluid, its sensitivity to each of the sulfonamides, to penicillin, and to streptomycin should be determined. The drugs found to be most powerful against the specific strain should be selected, and with such dosage as to secure blood levels (and consequently spinal fluid levels) well above the minimal sensitivity concentration.

When sensitivity tests cannot be made, or until these sensitivities have been determined, the treatment of choice should consist of large doses—at least 50,000 units every three hours—of penicillin intramuscularly (none needed intrathecally) and a sulfonamide in amounts of 2 to 3 grains per pound of body weight per day. The choice of the sulfonamide seems to be discretionary, except that there is strong evidence against the effectiveness of sulfanilamide. Therefore, one should prescribe either sulfadiazine, sulfathiazole, or sulfapyridine.

SUMMARY

1. We believe our review of the literature concerning *Streptococcic viridans* meningitis is the first to have been undertaken. Twenty-five recoveries and 26 deaths have been reported. To those we are able to add nine recoveries and three deaths. These were taken from recent records of Chicago Municipal Contagious Disease Hospital and Cook County Contagious Disease Hospital. The additions make a total of 34 recoveries and 29 known deaths following *Streptococcic viridans* meningitis. Six cases, with two recoveries, from the general wards of Cook County Hospital are also included in the tables of this article.

2. The bacteriology of the organism *Streptococcus viridans*, including criteria for laboratory diagnosis, is presented.

3. The incidence of *Streptococcic viridans* meningitis was found to be 0.3 per cent to 2.4 per cent of all cases of purulent meningitis.

4. The frequency of streptococcic meningitis of all types found in the sources available to us has decreased in the past five years. This may be a result of the decline of severe ear, nose, and throat infections and is often attributed to the use of the sulfonamides and antibiotics.

5. *Streptococcic viridans* meningitis has shown a relative increase when compared to the total number of cases of all types of streptococcic meningitis.

6. The probable sources of infection in *Streptococcic viridans* meningitis are analyzed. The disease followed subacute bacterial endocarditis in only 13 per cent of the cases; ear, nose, and throat infections in 31 per cent; and there was no source found (primary) in 35 per cent.

7. *Streptococcus viridans* organisms have been found to vary in their sensitivity to different sulfonamides and to penicillin. In addition, there are strains which are resistant either to various sulfonamides or to penicillin. We found no reports that any one strain was resistant to both the sulfonamides and to penicillin.

8. Therapy in *Streptococcic viridans* meningitis should be adjusted after

determination of the sensitivity of the organism isolated from the spinal fluid to all the sulfonamides and to the antibiotics.

9. Where sensitivity tests are not available, and prior to learning the results of these tests, the treatment of choice appears to be the use of a combination of penicillin and a sulfonamide. Penicillin should be given in large doses intramuscularly. Intrathecal medication is contraindicated, and repeated spinal punctures are seldom necessary. The sulfonamide should be given in dosage of 2 to 3 grains per pound of body weight per day, and may be either sulfathiazole, sulfadiazine, or sulfapyridine.

10. Five tables are presented which concern, respectively, recoveries, deaths, incidence, probable portal of entry, and frequency according to age groups.

CONCLUSION

Studies should be undertaken to determine definitely the sulfonamide of choice for the treatment of *Streptococcic viridans* infections. An effort should also be made to learn if there are any strains which are resistant to both sulfonamides and to penicillin. More investigations are desirable in regard to the possible value of streptomycin therapy.

CASE REPORTS

Case 1. A 6 year old white girl was admitted to Cook County Contagious Hospital September 21, 1944, with right hemiplegia, inability to talk, and a history of onset accompanied by sudden collapse occurring 18 hours previously. Her temperature was 101.4° F. On physical examination the heart was found to be moderately enlarged to the right and left with mitral configuration. There was a rough systolic murmur at the apex and base. The deep reflexes were absent on the right. A lumbar puncture revealed 1,300 cells, of which 90 per cent were polymorphonuclears. Smear was negative for organisms. The report on culture of the spinal fluid was that gram-positive diplococci, free and in short chains, were found; they were further identified as *Streptococcus viridans*. Spinal fluid chemistry disclosed chlorides 685 mg. per cent, proteins 45 mg. per cent, and glucose 62 mg. per cent. A second lumbar puncture was performed on September 23 and there were 900 cells per cu. mm. with 90 per cent polymorphonuclears. Culture of this fluid disclosed gram-positive diplococci, which were again diagnosed as *Streptococcus viridans*. The spinal chlorides were 789 mg. per cent; protein, 15 mg. per cent, and glucose, 48 mg. per cent. The child was treated with sulfathiazole, 1.0 gm. every four hours. There was fairly rapid improvement, with the temperature falling by lysis from 103° to normal in the first few days, but on September 27 there was a spike to 105°, rectally. This was felt to be central in origin, but sulfathiazole was stopped on September 29 and the patient started on sulfadiazine, 0.75 gm. every four hours. A third lumbar puncture on September 29 disclosed only 15 cells and culture was negative. Spinal chlorides were 700 mg. per cent; protein, 30 mg. per cent, and glucose, 81 mg. per cent. There was a rapid decline in temperature in a few days and the patient remained afebrile thereafter. Sulfadiazine was discontinued on October 7. All blood cultures were negative; one each on September 22, September 29, and daily cultures on October 2, 3, 4, 5, and 6. The patient was transferred to Cook County Children's Hospital October 9, with a discharge diagnosis of *Streptococcic viridans* meningitis, rheumatic heart disease, and residual right hemiplegia.

At the Children's Hospital the child continued afebrile until October 29, when she spiked a high fever and the spleen was palpable and tender. The patient was started on sulfadiazine and penicillin, 5,000 units every four hours. She continued to have a spiking temperature for the next few days and then was afebrile. Petechiae were never seen. Daily blood cultures on October 26, November 1, 2, 3, and 4 were negative. On December 5, penicillin was discontinued after 1,000,000 units had been given. The patient became febrile again December 29 and ran a low grade temperature for a few days. A rheumatic exacerbation with myocarditis and early decompensation was diagnosed at this time. Blood cultures were negative on December 18 and 24, 1944, and January 1 and 3, 1945. The patient's cardiac condition improved and she left the hospital February 11. At that time she was able to walk with a limp, and there was some atrophy of the right arm.

While this case may have been actually one of subacute bacterial endocarditis, the clinicians in charge felt that the substantiated diagnosis was rheumatic heart disease.

Case 2. A 29 year old white female was admitted to the Cook County Contagious Hospital September 5, 1945, having been transferred from the County Psychopathic Hospital, which she had entered the day prior. There was a history of chills at onset and repeated vomiting for three weeks. She became irrational the day before entry to the Psychopathic Hospital, and when admitted to the Contagious Hospital was irrational and thrashing about. A lumbar puncture at the Psychopathic Hospital on September 5 had disclosed many pus cells and a negative smear. Culture report: "Gram-positive diplococci, green zoning. Bile solubility: not dissolved, thus green streptococci." Admission blood culture was negative. The patient received 6.0 gm. of sodium sulfathiazole intravenously immediately and 2.0 gm. every four hours intravenously. On September 8 the dosage was reduced to 1.5 gm. every four hours and finally discontinued September 15. A spinal tap on September 8 disclosed 440 cells, predominantly polymorphonuclears. Culture was negative. Spinal glucose was 33 mg. per cent at this time, chlorides 660 mg. per cent, and protein 184 mg. per cent. The patient became afebrile September 9 and remained so thereafter. Nevertheless, she remained in a confused and disoriented state and was returned to the Psychopathic Hospital September 21, 1945, as a postmeningitic psychosis.

Case 3. A 33 year old white male was admitted to Cook County Contagious Hospital January 11, 1946, semi-rational, restless, with a temperature of 103° rectally and with the right tympanum inflamed and a white plaque found over the posterior-inferior quadrant. There was a history of a cold for 10 days, with spontaneous drainage from the right ear on January 7, 1946, which stopped abruptly January 10. A diagnostic lumbar puncture disclosed cloudy greenish fluid, with a cell count of 15,000. Immediately 40,000 units of penicillin were given intrathecally. Laboratory report: "Direct smear: gram-positive diplococci, free and in long chains. Culture confirmed smear green zoning. Bile solubility: not dissolved. Thus, green streptococci." Spinal fluid tests showed glucose 12 mg. per cent, chlorides 740 mg. per cent, and protein 370 mg. per cent. A repeat lumbar puncture on January 14 disclosed cloudy fluid with 2,250 cells. The smear and culture were negative. Spinal fluid glucose at this time was 27 mg. per cent, chlorides 720 mg. per cent, and protein 200 mg. per cent. Admission blood culture was negative.

The patient received 5.0 gm. of sodium sulfathiazole intravenously, followed by 2.0 gm. every four hours intravenously. Penicillin was given intramuscularly, 30,000 units every three hours, and was discontinued January 22. Sulfathiazole was reduced to 1.5 gm. every four hours orally January 13 and discontinued January 24. The temperature gradually subsided and became normal by January 16 and remained so.

Double vision was noted on January 16 and the patient was discharged January 25, 1946, with a moderate bilateral rectus paresis.

Case 4. A 45 year old Negro woman admitted to Cook County Contagious Hospital January 12, 1946, was delirious and restless, with slight opisthotonos; temperature 105° F., and a discharging left ear. Admission lumbar puncture disclosed 16,800 cells (predominantly polymorphonuclears), and gram-positive diplococci, free and in chains, on direct smear. Forty thousand units of penicillin were given intrathecally. Spinal fluid glucose was 24 mg. per cent, protein 370 mg. per cent, and chlorides 695 mg. per cent. Culture report on spinal fluid: "Gram-positive diplococci free and in chains. Green zoning. Bile solubility: not dissolved. Thus, green streptococci." Blood culture on admission: no growth. A second lumbar puncture on January 14 disclosed 1,350 cells, no organisms on direct smear, and a negative culture; 30,000 units of penicillin were given intrathecally on this date. Spinal fluid glucose was 31 mg. per cent, protein 200 mg. per cent, and chlorides 650 mg. per cent. Culture of the left ear discharge revealed a few colonies of staphylococcus.

The patient was treated with sodium sulfathiazole, 5 gm. intravenously and 2.0 gm. every four hours intravenously. Penicillin was administered intramuscularly in dosage of 30,000 units every three hours. The sulfathiazole was reduced to 1.0 gm. every four hours on January 17, and the pe..icillin to 10,000 units every three hours. Rapid improvement took place and the temperature was normal on January 15, and remained so. A transient diplopia was noted January 19. The patient was discharged January 25, 1946.

Case 5. An 11 month old white female was admitted to Cook County Contagious Hospital January 1, 1947, having developed a fever with projectile vomiting after feedings three days before. For the two previous days the infant had been listless and lethargic. On admission the temperature was 103° rectally. The infant was irritable when handled but otherwise was listless and had a fixed stare. Ear, nose, throat, and chest examinations were negative. A lumbar puncture revealed 460 cells, predominantly lymphocytes, and a few organisms on direct smear. Culture report: "Gram-positive diplococci, free and in short chains. Bile solubility: not dissolved. Subculture—green streptococci." Blood culture was negative. Spinal fluid tests disclosed glucose 10 mg. per cent and protein 500 mg. per cent. The patient was treated with sodium sulfathiazole, 1.0 gm. subcutaneously and 0.5 gm. every four hours subcutaneously, and penicillin 20,000 units every three hours. The patient became afebrile January 4, but irritability remained until January 9. The sulfonamide was given orally by January 4 and reduced to 0.5 gm. every six hours on January 6, and discontinued January 10. Penicillin was stopped January 13 and the patient discharged January 17, 1947, after a rapid recovery.

Case 6. A 9 year old white girl was admitted to Municipal Contagious Disease Hospital October 21, 1938, with a history of having had an earache October 14 with subsequent discharge. On the day of admission the patient had nuchal rigidity, was irrational, vomited, and had a temperature of 105° rectally. It was noted that the left tympanum was slightly injected with a recently healed perforation scar. Lumbar puncture revealed very cloudy fluid containing 10,000 cells, predominantly polymorphonuclears and a few gram-positive diplococci on direct smear. On culture, gram-positive diplococci, identified as *Streptococcus viridans*, were reported. Culture of the left ear canal was negative. Treatment consisted of sulfanilamide, 3.0 gm. subcutaneously, and then 1.0 gm. every four hours subcutaneously. On October 23 this was reduced to 0.67 gm. every four hours. By October 25 the patient, though still somewhat irritable, was rational. However, a temperature of 103° rectally persisted and left tympanum was found to be red and bulging. A myringotomy was performed, with release of purulent sanguineous fluid which revealed *Staphylococcus albus* on culture. There was a daily afternoon temperature rise from October 24

to 27, and a repeat lumbar puncture performed on October 27 revealed 2,000 cells, negative smear, but *Streptococcus viridans* was again recovered on culture. The spinal fluid glucose at this time was 30 mg. per cent. A blood culture taken this day during a chill revealed no growth. The patient gradually improved, there being an occasional rise of temperature to 101 to 102° the following week but a return to normal by October 30. On November 3 the sulfanilamide was reduced to 0.3 gm. every four hours, and the patient was discharged November 9, 1938.

Case 7. A seven and one-half year old white boy admitted to Municipal Contagious Disease Hospital April 14, 1944, had a history of onset of illness April 4, 1944, with vomiting and headache. The following day a physician diagnosed a bilateral otitis media and prescribed a sulfonamide. The patient continued to have a temperature of 104° rectally and to vomit, and on April 12 a left myringotomy was performed. On the night of April 13 the boy became delirious; the temperature was 105° rectally and he had a convulsion. When he entered the hospital his temperature was 105° rectally; he was rational though uncoöperative, and on examination the left tympanum was red and bulging, with a small perforation present. The right tympanum was injected but retracted. No mastoid tenderness was present. Lumbar puncture revealed only 325 cells, predominantly polymorphonuclears; no organisms were seen on direct smears, but the culture report was: "Gram-positive organisms in chains, which failed to type by direct Neufeld and further identified as *Streptococcus viridans.*" Spinal fluid tests showed sugar, 85 mg. per cent; protein, 45 mg. per cent, and chlorides, 716 mg. per cent. The boy was given 2.0 gm. of sodium sulfadiazine intravenously and 0.5 gm. every four hours intravenously. The patient became irrational and restless the next day but showed some improvement thereafter. However, on April 20 he became stuporous, had severe convulsions and developed a profuse discharge from the left ear. (Culture of this discharge disclosed no streptococci.) Again, 3.0 gm. of sodium sulfadiazine were given intravenously and 1.0 gm. every four hours. A day later the patient was able to take his medication orally. On April 23 there was some left mastoid tenderness. Improvement continued and sulfadiazine was discontinued April 26. But on April 30, though afebrile, headache returned and nuchal rigidity was present. Therefore, 2.0 gm. of sulfadiazine were given and 1.0 gm. every four hours. Medication was discontinued on May 3 and the patient was discharged May 5, 1944.

This patient was examined by one of us February 25, 1948, four years after his illness. He was found to be in good health and progressing well in grade school. There were no neurologic signs, and no abnormalities of the heart or lungs were found. Some slight scarring of the left tympanum was present. The parents related that the first three years after hospital discharge the boy would have occasional headaches with vomiting. There were also some increased irritability and social withdrawal tendencies. In school he demonstrated poor powers of concentration. These mental abnormalities have since subsided.

Case 8. A five month old white male was admitted to Municipal Contagious Disease Hospital June 5, 1945, with a stiff neck, positive Kernig's, temperature of 101° rectally, and a draining sinus at the base of the spine. A lumbar puncture revealed 10,200 cells, with gram-positive diplococci on smear. A culture of the fluid grew out gram-positive cocci in pairs and in short chains, which produced green pigmentation on blood agar, failed to type by direct Neufeld, and was bile insoluble. The organism was thus determined to be *Streptococcus viridans.* The spinal fluid tests showed glucose 20 mg. per cent, proteins 156 mg. per cent, and chlorides 731 mg. per cent. Admission blood culture was negative. The infant received sulfadiazine, 2.0 gm. initially and 0.5 gm. every four hours, and penicillin, 10,000 units every two hours. A repeat lumbar puncture was performed June 8 and disclosed 1,200 cells and a few gram-positive cocci on smear. Culture again was positive for *Streptococcus viridans.* Ten thousand units of penicillin were given intrathecally at this time. The spinal

sugar was 19 mg. per cent, protein 438 mg. per cent, and chlorides 724 mg. per cent. The patient improved gradually, having a slowly declining fever level but a spiking temperature of 102 to 103° rectally from June 5 to 11. The infant remained afebrile from June 12 to July 12, but in spite of the clinical improvement at this time, *Streptococcus viridans* was again cultured after lumbar puncture on June 20, when there was a spinal cell count of 1,020, with predominance of lymphocytes. No organisms were found on smear, however. A repeat blood culture on June 25 was negative. Sulfadiazine was discontinued on June 15 and penicillin was discontinued July 5. Measurements at this time indicated that no increase in head circumference had taken place.

On July 13, the baby became irritable again, had a stiff neck and a bulging fontanel, and suddenly developed an elevated temperature. Sulfadiazine, 2.0 gm., was administered, and then 1.0 gm. every four hours was given and 10,000 units of penicillin every two hours were resumed. The sulfadiazine was reduced to 0.5 gm. every four hours on July 16 and finally discontinued on July 18, the infant having become afebrile July 16. Blood culture taken July 17 was negative. The patient became febrile again July 20, running a fever of 103° rectally. Sulfathiazole, 0.5 gm. every four hours, was started but was without effect and was discontinued July 25. It had been noted July 22 that there were absent deep quadriceps tendon reflexes, no apparent sensation in the legs, and that the legs were flexed and drawn up to the body. Another lumbar puncture on July 23 and a cisternal puncture on July 26 revealed no growth on spinal fluid culture, and on July 26 there were only 12 cells, with spinal fluid glucose 53 mg. per cent, chlorides 708 mg. per cent, and protein 100 mg. per cent. The temperature remained between 103 and 104° rectally after its rise on July 20. It was felt that the clinical picture was the result of an epidural abscess of the lower spinal canal, the meningitis having been cured. The patient on August 2 was transferred to another hospital for surgery. We saw this patient some months after his operation. He appeared to be in good health and was able to walk.

Case 9. A 6 month old Negro male was admitted to Municipal Contagious Disease Hospital October 27, 1947, having had a fever and vomiting for four preceding days. Examination disclosed a lethargic, severely ill and toxic baby who did not even respond to painful stimuli. The temperature was only 98.6° rectally. Lumbar puncture revealed opalescent fluid, with a cell count of 630, and on smear gram-positive diplococci, free and in short chains, were found. A culture yielded gram-positive diplococci resembling pneumococci. These organisms produced green hemolysis on blood agar, but failed to type by direct Neufeld and were bile insoluble; thus were identified as *Streptococcus viridans*. The spinal fluid glucose was 16 mg. per cent, protein 174 mg. per cent, and the chlorides were 714 mg. per cent. Therapy consisted of sulfadiazine, 2.0 gm. subcutaneously at once and 0.5 gm. every four hours, with penicillin, 30,000 units every three hours. Sulfadiazine was reduced to 0.25 gm. every four hours on October 29, but when the blood sulfadiazine level fell to 3.5 mg. per cent the dosage was increased to 0.5 gm. every four hours on November 1. After a few days during which the patient seemed moribund and had bilateral clonic convulsions there was gradual improvement. The temperature slowly declined and the patient became more alert and less irritable. However, after a few afebrile days, on November 9 the temperature spiked to 104° rectally and continued at 100 to 101° rectally. Sulfadiazine was discontinued as without effect, and a lumbar puncture was repeated on November 11 which revealed 6,500 cells and no organisms on direct smear, but *Streptococcus viridans* was again recovered on culture. (Blood culture on this date was negative.) Spinal fluid glucose was 27 mg. per cent, chlorides 704 mg. per cent, and protein 140 mg. per cent. With these spinal fluid findings present, penicillin was increased to 100,000 units every three hours and sodium sulfathiazole was given subcutaneously, 1.25 gm. every eight hours. During the next week the temperature

leveled at 100 to 101° rectally, but there was opisthotonos, listlessness, and lethargy, and there were a few generalized convulsions. On November 14, sodium sulfathiazole was given, 0.5 gm. every four hours intravenously, Streptomycin, 0.1 gm. every three hours, was started in the hope that it might possibly be of some aid, and continued until November 20 without any special effect being apparent. Later there was gradual improvement, and a lumbar puncture on November 18 disclosed only 20 cells, and the spinal fluid culture was negative. Spinal fluid glucose was 51 mg. per cent, protein 39 mg. per cent, and chlorides 754 mg. per cent. In spite of these findings, the patient experienced a generalized convulsion on November 19 and became semi-comatose. But the next day the baby was afebrile and remained so until discharge. There was slow improvement, diminished irritability, and less lethargy. Oral medication was possible by November 23 and sulfathiazole was discontinued on November 25, with penicillin being reduced to 50,000 units every three hours. On November 30 penicillin was discontinued, and the baby was discharged December 10. The head circumference had not increased during the hospital stay, and the infant had gained two pounds in weight.

The child was seen again at his home on February 24, 1948, being then 10 months old. He had continued afebrile, had been gaining weight, and was non-irritable and playful. Neurologic examination revealed no abnormalities, and ear, nose, throat and chest were negative. The child was able to sit by himself and to stand with assistance. The anterior fontanelle was patent, measured 1.5 cm., and there was no bulging. The head circumference was 45 cm. and the chest circumference 45.7 cm. There had been an increase in head circumference of only 1.5 cm. in the previous four months.

Case 10. A 43 year old white woman was admitted to Cook County Contagious Hospital January 30, 1946, semi-comatose, blood pressure 240/120 mm. Hg and with slight injection but no bulging of the left tympanum. She had had a cold and an earache four days prior to admission and had received oral penicillin and sulfathiazole prescribed by her physician. She developed a stiff neck and became stuporous the day before admission. Our lumbar puncture revealed 2,800 cells and gram-positive diplococci, free and in chains, on smear. Culture disclosed gram-positive diplococci, free and in chains, with green zoning on blood agar, which were bile insoluble and identified as a "green streptococcus." Spinal fluid glucose was 22 mg. per cent, chlorides 690 mg. per cent, and protein 164 mg. per cent. Therapy consisted of sodium sulfathiazole, 7 gm. initially and 1.0 gm. every four hours for three doses and then 2.0 gm. every four hours. The temperature rose from 101.6° rectally at the time of admission to 103.4° rectally, and the patient died January 31, 1946, 27 hours after entering the hospital.

Case 11. A 48 year old Negro male was admitted to Cook County Contagious Hospital January 24, 1946, disoriented but obedient and having been ill since January 16 with pain in his low back. He developed chills and fever January 18 and headache and hallucinations on January 21. Admission lumbar puncture revealed thick purulent fluid with gram-positive diplococci, free and in chains, on direct smear. On culture there were recovered gram-positive diplococci, free and in chains, which produced a green zoning on blood agar and which were bile insoluble and identified as "green streptococci." Spinal fluid glucose was 17 mg. per cent, chlorides 715 mg. per cent, and protein 300 mg. per cent. Twenty thousand units of penicillin were given intrathecally following the admission tap. Other therapy consisted of sodium sulfadiazine, 7.0 gm. immediately and 1.0 gm. every four hours intravenously. A second lumbar puncture on January 28 revealed milky white spinal fluid. No organisms were found on smear or culture. Spinal fluid glucose at this time was 21 mg. per cent, and the protein was 354 mg. per cent. Forty thousand units of penicillin were given intrathecally, shortly after which the patient experienced generalized convulsions. Penicillin, 20,000 units every three hours intramuscularly, was also started. The patient responded poorly to therapy, the temperature remaining between 101° rectally and

102°; on January 30 there were constant twitchings of the body and the patient died, seven days after admission.

Case 12. A 51 year old Negro male was admitted to Cook County Contagious Hospital December 29, 1943, stuporous and with four plus nuchal rigidity; a systolic murmur was heard at the apex of the heart. There was a history of occipital and frontal headache for two weeks and drowsiness for three weeks. A purulent fluid was obtained by lumbar puncture which revealed chiefly polymorphonuclears and long chains of gram-positive cocci on smear. In culture, the organisms were identified as *Streptococcus viridans.* The spinal sugar was reported as being too low for determination, proteins 315 mg. per cent, and chlorides 690 mg. per cent. The patient received sodium sulfathiazole intravenously, 5.0 gm. at once and 2.0 gm. every four hours. There was no response on the part of the patient, who remained moribund from the time of admission. The temperature spiked between 101 and 104° rectally. He died January 6, 1947, seven days after admission.

Postmortem findings: Acute diffuse suppurative meningitis; embolic encephalomalacia; subacute, ulcerative and vegetative endocarditis of mitral valve; suppurative myocarditis; embolic glomerulonephritis.

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APICAL DIASTOLIC MURMURS IN PATENT DUCTUS ARTERIOSUS *

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For several years the authors have been interested in the occurrence of apical diastolic murmurs in some patients with patent ductus arteriosus. Recently the opportunity was presented of studying a group of 21 patients with patent ductus arteriosus, and the results of this study are presented in this paper. The apical diastolic murmurs with which we have been impressed sound to us like those that are encountered in mitral stenosis. They are low-pitched, rumbling murmurs, localized at the cardiac apex and best heard in the lateral decubitus after exercise.

A review of the English literature since 1895 yielded only five references to the occurrence of apical diastolic murmurs in patent ductus arteriosus. In 1940 Blumer and McAlenney [1] reported a case of patent ductus arteriosus with a diastolic murmur over the lower precordium. This is the limit of this description. At the autopsy of this patient a normal mitral valve was found. In 1940 Jones, Dolley and Bullock, [2] in describing several cases of patent ductus arteriosus, mentioned an apical diastolic murmur in four and state that, in two of these, the finding had led to a previous diagnosis of mitral stenosis. In 1941, Eppinger, Burwell and Gross [3] very definitely described an apical mid-diastolic murmur in one case of patent ductus arteriosus which disappeared following ligation. In 1945 Honigman and Brantigan [4] described a presystolic apical thrill and a late diastolic murmur in one patient with a patent ductus arteriosus and stated that this murmur disappeared after ligation. Levine and Geremia [5] state that in four of 37 cases "a definite mid-diastolic murmur was audible, quite unlike the diastolic murmur heard in the pulmonic area and resembling a murmur of mitral stenosis." In an instance of patent ductus arteriosus not recorded in the literature, [6] a soft blowing systolic murmur well transmitted into the left axilla and a low rumbling diastolic murmur sharply limited to the apex were heard; at autopsy a normal mitral valve was found.

MATERIAL

All of the patients had an unquestioned diagnosis of patent ductus arteriosus as recognized either by classical physical findings, operation, or both. Table 1 summarizes the 12 patients with patent ductus arteriosus who had no apical diastolic murmurs, and table 2 summarizes the findings in the nine patients who showed apical diastolic murmurs. Table 3 contrasts the sig-

TABLE I

12 Cases of Patent Ductus Arteriosus *without* Apical Diastolic Murmurs
(Only Recorded Notations Considered)

Patient	A. D.	C. T.	C. K.	J. O.	A. S.	J. E.	T. B.	B. D.	D. D.	M. D.	K. G.	R. H.
Sex	F	F	F	F	F	F	M	F	F	F	F	M
Age	5	5	10	10	10	9	3	2	16	7	7	16
History of rheumatic fever	0	0	0	0	0	0	0	0	0	0	0	0
Symptoms of cardiac embarrassment	0	0	0	0	0	+	0	0	0	0	0	0
Nutrition and development	N	N	N	N	Poor	N	N	N	N	N	N	N
Blood pressure (not after exercise)		118/25			116/50	110/68			110/50	125/70	112/60	100/60	144/62
Pulmonic second sound increased		+			+	+				+	+	+	+
Enlarged pulmonary artery	0	0	+	+	+	0	+	0	0	0	0	+
Increased pulsations pulmonary artery	+		+	+	+		+		0	0		
Left ventricular enlargement	0	0	0	0	?	0	0	0	0	0	0	0
Electrocardiogram	N	N	N	N	N	N	N	N	N	N	N	N

N = Normal.

nificant findings in the group of patients with and without apical diastolic murmurs. Case 4 (J. C.) is omitted from this table because her diastolic murmur persisted following operation and was apparently due to a rheumatic mitral stenosis. The most significant points of comparison are starred. Poor nutrition, cardiac enlargement, cardiac symptoms, and enlargement of the pulmonary artery were much more frequent in the group with apical diastolic murmurs than in the group without these murmurs.

The following case histories are presented because, in addition to illustrating the important clinical findings, phonocardiograms were obtained showing the diastolic murmurs.

CASE REPORTS

Case 1. A 13 year old white girl was admitted to the Colorado General Hospital on October 21, 1945. A heart murmur had been discovered at the age of 22 months. Fatigue and shortness of breath upon slight exertion became evident at the age of seven. No cyanosis or edema had been present at any time.

On examination, blood pressure was found to be 100 mm. Hg systolic and 54 diastolic. Over the base of the heart a thrill was evident. In the first and second interspaces on the left, a loud machinery-like murmur was present (figure 1). At the apex and just lateral to the apex, the heart sounds were accentuated and a systolic murmur and a mid-diastolic murmur were present. The mid-diastolic murmur had the low-pitched rumbling character of the mid-diastolic murmur heard in mitral stenosis and was in the usual location. It was accentuated in the left lateral decubitus after exercise (figure 2).

TABLE II

Nine Cases of Patent Ductus Arteriosus *with* Apical Diastolic Murmurs
(Only Recorded Notations Considered)

Patient	C. R.	R. S.	A. T.	C. M.*	E. H.	J. S.*	C. L.*	M. B.*	J. C.‡
Sex	F	F	F	F	M	F	M	F	F
Age	9	9	13	10	9	12	8	3	9
History of rheumatic fever	0	0	0	0	0	0	0	0	Vague
Symptoms of cardiac embarrassment	0	+	+	+	Asthma	+	+	0	0
Nutrition and development	N	Poor	Poor	Poor	Poor	N	Poor	Poor	Fair
Blood pressure (not after exercise)	108/50	122/80	110/55	108/40	128/68	100/54	125/45	108/38	130/65
Pulmonic second sound increased	+	+	+	+		+	+	+	+
Timing of diastolic murmur	Mid	Mid	Mid	Late	Mid	Mid	Mid	Mid Late	Mid Late
Enlarged pulmonary artery	+	+	+	+	+	0	+	+	+
Increased pulsations pulmonary artery	+		+	+			+	+	
Left ventricular enlargement	0	+	+	+	0	+	+	+	+
Electrocardiogram	N	LAD	N	N	N	N	N	LAD	N

* Duct ligated and diastolic murmur disappeared.
‡ Duct ligated and diastolic murmur did not disappear.

TABLE III

Comparison of Cases *with* and *without* Apical Diastolic Murmurs
(Numbers in parentheses indicate number of cases in which actual notation of presence or absence of the information in question has been made.)

	Eight Cases *with* Apical Diastolic Murmurs		Twelve Cases *without* Apical Diastolic Murmurs	
	Number	Per Cent	Number	Per Cent
Males	2 (8)	25	2 (12)	17
Females	6 (8)	75	10 (12)	83
Average age	9.1 (8)		8.3 (12)	
Cardiac symptoms present	5 (7)	71*	1 (12)	8.3*
Poor nutrition	6 (8)	75*	1 (12)	8.3*
Average pulse pressure	59 (8)		58 (8)	
Pulmonic second sound accentuated	7 (7)	100	7 (7)	100
Pulmonary artery enlarged	7 (8)	88*	5 (12)	42*
Pulmonary artery pulsations increased	5 (5)	100	5 (7)	71
Left ventricle enlarged	6 (8)	75*	0 (12)	0*

* Figures of considered significance.

The patient was operated upon on October 26, 1945, and a patent ductus about 1.5 cm. wide and 0.75 cm. long ligated. Examination on several occasions following the operation has revealed the absence of all murmurs (figure 1, figure 2).

Case 2. An eight year old white male entered Colorado General Hospital on November 3, 1947. He had had a known cardiac abnormality for years. Weakness and fatigue had been present all his life.

Examination revealed a pale, undernourished boy, somewhat small for his age. The blood pressure was 125 systolic and 45 diastolic. The heart was moderately enlarged to the left. A thrill was present in the third interspace to the left of the sternum. A loud, continuous, machinery-like murmur with systolic accentuation was present in the first, second, and third interspaces to the left of the sternum. No clear first sound could be heard in this area. The second sound was accentuated. At the apex the diastolic murmur heard at the base was no longer evident, but a
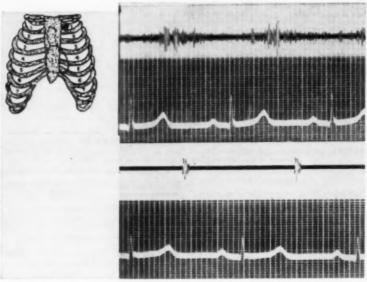
FIG. 1. *Case 1.* Chest piece in first interspace just to left of the sternum. Upper tracing, before ligation, shows the machinery-like murmur. Lower tracing shows its disappearance after ligation.

clear-cut mid-diastolic murmur of low pitch and best heard in the left lateral position was present. Sound records (figure 3) show that when the heart rate increased this murmur extended almost to the first sound. Since the first sound was not accentuated, the impression of a presystolic accentuation of the murmur did not occur.

On November 12, 1947, the patient was operated upon and a patent ductus arteriosus about 8 mm. in diameter was ligated. On dismissal a 2 plus systolic murmur of low to medium pitch could be heard at the base and a 1 plus systolic murmur at the apex. No diastolic murmurs were present (figure 3).

Case 3. A three year old white girl entered Colorado General Hospital on December 8, 1947. The patient's mother had had rubella when three and one-half

months pregnant and the child was born, at full term, with a heart murmur, anemia, and bilateral cataracts.   She was a feeding problem from infancy and it was not until the age of 18 months that she could swallow solid foods without regurgitation. Her difficulty seemed to be with swallowing.   Weakness, fatigue, and under-development had always been present.

On examination the patient appeared quite retarded mentally.   No edema, cyanosis, or clubbing of the fingers was present.   The blood pressure in the right arm was 74 systolic and 32 diastolic, and in the left arm 108 systolic and 38 diastolic.
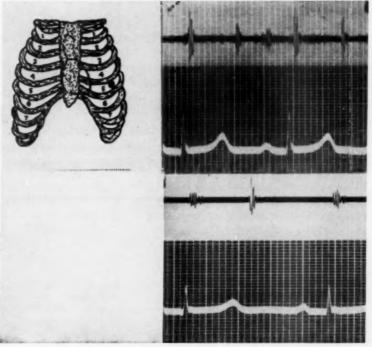
Fig. 2. *Case 1*. Chest piece in fifth interspace just outside midclavicular line. Amplification increased over figure 1. Patient in the left lateral decubitus after exercise. Mid-diastolic murmur very evident. Murmurs gone after ligation.

The blood pressure in the legs was 118 systolic and 42 diastolic.   A systolic thrill could be felt in the second left interspace.   In the first, second, and third interspaces to the left of the sternum a loud, rough systolic murmur was present.   The first heart sound was faint and the second heart sound accentuated (figure 4).   At the apex a loud first sound was followed by a rough systolic murmur of an intensity less than that of the systolic murmur at the base.   Following a clear second sound there was a short silent interval and then a mid-diastolic murmur which, because of the rapid heart rate, was short and followed by a clear pre-systolic murmur (figure 4).

Roentgenography of the heart revealed enlargement to the left with increased

prominence of the pulmonary artery. There was also a depression of the posterior esophageal wall slightly above the aortic arch which was interpreted as due to an anomalous blood vessel.

Patient was operated upon on December 23, 1947. A patent ductus about 1 cm. in diameter was found in the usual position. The origin of the right subclavian artery was posterior and just distal to the left subclavian artery. From this origin it passed behind the esophagus and produced some esophageal obstruction. The right subclavian artery and then the patent ductus were ligated. The patient left the operating room in excellent condition. En route to the ward, the patient sud-
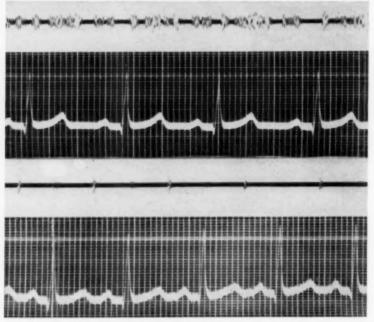
FIG. 3. *Case 2.* Chest piece at apex. Upper tracing, before ligation, shows a faint first heart sound, a systolic murmur with somewhat of a crescendo character, a loud second sound, an early diastolic silent period and a mid-diastolic murmur. When diastole is short the murmur extends through auricular contraction almost to the first sound. The lower tracing shows the disappearance of the diastolic murmur after ligation.

denly ceased breathing and her pulse could not be obtained. She was returned to the operating room and the incision reopened. The ligature on the proximal end of the divided subclavian artery was found to have slipped off, filling the chest with blood. With rapid infusion of 450 c.c. of whole blood, replacement of the ligature, and cardiac massage, the heart resumed beating and the child began to breathe without artificial respiration. Four hours after the operation the respirations were regular and the blood pressure was 120 systolic and 80 diastolic. She was still comatose and hyperspastic. During the next 10 hours her blood pressure gradually fell and the pulse rate increased. She died 15 hours after resuscitation. Ausculta-
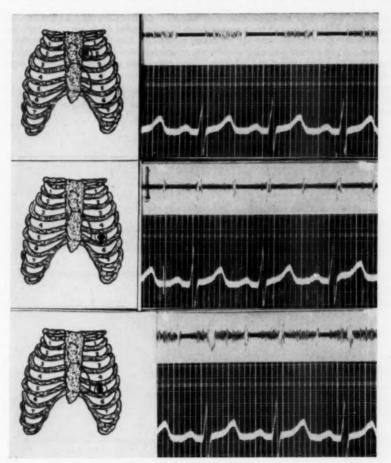
Fig. 4. *Case 3.* *Upper.* Chest piece in the second interspace just to left of the sternum. A faint first sound is followed by a loud systolic murmur and an accentuated second sound. No definite diastolic murmur. *Middle.* Chest piece in fifth interspace in midclavicular line. Same amplification. A loud first sound is followed by a systolic murmur and a moderately loud second sound. A silent period in early diastole is followed by a mid-diastolic murmur with a presystolic accentuation. *Lower.* Same as *middle* but at greater amplification.

tion of the heart during the period after the operation revealed the absence of murmurs.

On postmortem examination the heart was obviously enlarged, weighing 100 gm. (normal 73 gm.). The endocardium was smooth and translucent with thin normal-appearing valve cusps. The valve circumferences were: tricuspid, 5.5 cm.; pulmonic, 3.5 cm.; mitral, 5.5 cm.; and aortic, 3 cm. The ductus arteriosus was 1.2 cm. long and 1 cm. in diameter. The aortic arch gave rise to four main trunks as described above.

Case 4. A nine year old white girl entered Colorado General Hospital on September 27, 1944. She had been cyanotic for 12 hours after birth but then had done quite well. During the first six to seven months of life she became cyanotic on crying. At two years and nine months she was hospitalized because of high colored scanty urine following an ear infection. For some time previous to hospitalization
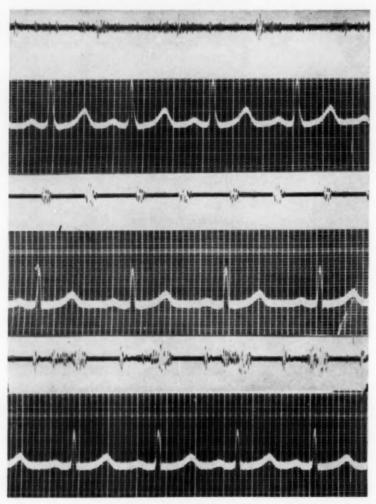
Fig. 5. *Case 4. Upper.* Chest piece in second interspace just to left of the sternum. A loud murmur is present extending through systole and diastole. *Middle.* Same area after ligation. Faint systolic murmur is still present. Diastolic murmur is gone. *Lower.* Chest piece at apex. After ligation, a mid-diastolic murmur with presystolic accentuation is still present.

there had been some pains in the back and legs. Examination at this time revealed a systolic murmur along the left side of the sternum. At three and one-half years of age a note was made of the presence of a machinery-like murmur at the base of the heart.

On admission to the hospital the chief complaint was fatigue of several months' duration. Frequent epistaxis had been present. Blood pressure was 130 systolic and 65 diastolic. In the first, second, and third interspaces to the left of the sternum a loud machinery-like murmur extending through systole and diastole was present (figure 5). At the apex the most striking feature was a mid-diastolic rumbling murmur which continued to the first sound with a late diastolic accentuation. The diastolic murmur was entirely different from the diastolic murmur heard at the base. A high-pitched systolic murmur of lower intensity was also present at the apex.

On October 6, 1944, the patient was operated upon and a patent ductus was ligated. Two months later auscultation revealed a low-pitched systolic murmur in the second and third intercostal spaces on the left. No diastolic murmur was now present in this area (figure 5). At the apex the mid-diastolic murmur with pre-systolic accentuation and loud first sound were still present (figure 5). A high pitched systolic murmur was still present at the apex.

This girl apparently had a combination of rheumatic heart disease and congenital heart disease.

DISCUSSION

It is evident from the foregoing data that, if looked for consistently, apical diastolic murmurs resembling the murmur of mitral stenosis are found in a high percentage of cases of patent ductus arteriosus. Three factors may play a part in the production of these murmurs: (1) Enlargement of the left ventricle, which frequently results from the altered mechanics produced by the shunt from the aorta to the pulmonary artery, produces a relative mitral stenosis. (2) As a result of the shunt, much more blood flows through the left side of the heart and the speed of blood flow through the mitral valve is greatly increased, making the occurrence of a murmur more likely. (3) In children, possibly because of thinner chest walls and thinner ventricular musculature, the flow of blood into the ventricles during diastole seems normally more likely to produce some sound.

A common cause of murmur production is the sudden widening of the blood stream, with the blood flowing from a high pressure to a low pressure area. This is the accepted explanation of the diastolic murmurs that are heard in mitral stenosis. During diastole the narrowed mitral ring accentuates the difference between the high pressure of the left auricle and the low pressure of the left ventricle, and also narrows the blood stream just before the flow enters the wider cavity of the latter chamber. Apical diastolic murmurs also occur in patients who have relative mitral stenosis. In such cases, while the size of the mitral ring is normal, the cavity of the left ventricle is sufficiently enlarged that the same mechanical conditions pertinent to true mitral stenosis exist. In 1923 Wood and White [7] emphasized this in a paper in which they pointed out the frequency of apical mid-diastolic murmurs in instances of dilatation of the left ventricle (anemia, hypertension, etc.). Later, in 1935, Bland, White and Jones [8] emphasized the same

thing, largely on the basis of their own experience with acute rheumatic carditis.

Eppinger, Burwell and Gross [8] have carefully studied the effects of the aorta-pulmonary shunt of patent ductus arteriosus and its mechanical effects upon the heart. These investigations stressed the increased blood flow through the pulmonary circulation resulting from the shunt from the aorta to the pulmonary artery. This increased volume of blood returns to the left auricle and then passes through the mitral ring to the left ventricle, from whence it is pumped again into the aorta where the cycle begins again. This means that the left ventricle pumps considerably more blood than the right, the increase depending upon the size of the patent duct. A high degree of shunt was demonstrated, from 45 to 75 per cent of all of the blood entering the aorta returning to the pulmonary circulation. This meant that the left ventricle was pumping from two to four times the output of the right. Shapiro, Keys and Violante,[9] by combining the acetylene and roentgen-kymographic methods in the intact and unanesthetized human being with patent ductus arteriosus, demonstrated shunts that represented an average of from 20 to 60 per cent of the aortic blood volume. Dexter [10] describes a patient in whom the flow through the shunt, as determined by venous catheterization of the heart, was 65 per cent of the aortic blood volume.

The large output of the left ventricle results in a greater diastolic size of the ventricle. The increased work done by the left ventricle over a period of years results in left ventricular hypertrophy and eventually dilatation. The enlarged ventricular cavity distal to a normal mitral ring creates the situation of relative mitral stenosis and sets the stage for the production of diastolic murmurs. Table 3 indicates that apical diastolic murmurs in patent ductus arteriosus are most likely to occur in the presence of cardiac symptoms and cardiac enlargement, and thus emphasizes the relationship of these murmurs to enlargement of the left ventricle.

The speed of blood flow from a high to a low pressure area, particularly through a stenosed mitral valve, is of great importance in determining whether a murmur will be produced. A very mild degree of stenosis may produce no murmur in a patient at rest and a very obvious murmur after the patient exercises, or if the patient has a fever. A patient has been studied [11] who had no cardiac murmurs while in a state of profound myx-edema with an enlarged cardiac silhouette. After treatment with thyroid, a moderately loud diastolic murmur characteristic of mitral stenosis became evident, although the heart decreased in size. It has been shown [12] that in the myxedematous state the cardiac output is markedly decreased (40 to 50 per cent) and the velocity of blood flow decreased. The velocity of blood flow is often so slow that, even though the circulatory needs of the body are markedly lowered, the arteriovenous oxygen difference is increased. With thyroid therapy the cardiac output and the speed of blood flow return to normal. In this patient the importance of the speed of blood flow in

the production of the murmur is indicated by the fact that the murmur occurred after therapy in spite of a decrease in the relative size of the ventricle to the mitral ring.   Since the blood flow through the mitral ring in patent ductus arteriosus may be two or more times normal, the tendency to the production of diastolic murmurs is accordingly greatly increased.

In listening to many children, the authors have been impressed with the sounds that can occasionally be heard in diastole in thin-chested children.   A third heart sound is frequently heard in children.   In some instances the third sound seems to be prolonged or followed by other sounds to a sufficient degree to give the listener the   impression of a very short mid-diastolic rumble.   The same rumble occurring in an adult might be considered abnormal and evidence of a mitral stenosis.   In many children, especially with the heart working under stress (excitement or exertion), the flow of blood through the mitral valve may well be close to the threshold of sound production.   A murmur would then readily result if other factors favoring murmur production were added.   In patent ductus arteriosus the additional factors would be the enlarged left ventricle and the increased blood flow through the mitral valve.

The proposed explanation for the apical diastolic murmurs should account for the presence of both mid-diastolic and presystolic murmurs, since both have been demonstrated phonocardiographically.   In organic mitral stenosis, ventricular filling is decreased during diastole due to the narrowed mitral valve.   When the enlarged and hypertrophied auricle contracts, it is an effective agent in forcing blood into the ventricle under pressure and the presystolic murmur is produced.   In patent ductus arteriosus the mitral valve is of normal size, and ventricular filling should be rapid and occur mainly during the period immediately following the opening of the auriculo-ventricular valves.   A presystolic murmur might not be expected in a heart beating at a rate slow enough for the ventricles to be full at the time of auricular contraction.   If, however, the heart rate is so rapid that auricular contraction occurs relatively early in diastole and is superimposed on the phase of rapid diastolic inflow, auricular contraction may be effective in increasing the flow into the ventricle.   The mid-diastolic and presystolic murmurs will be merged and the amount of mid-diastolic murmur present will depend on the heart rate (figure 4).   Aside from the possibility of a short diastole being a factor in the appearance of a presystolic murmur, another consideration enters the picture which may be of importance.   The greater volume of blood which flows through the mitral valve in patent ductus arteriosus must take a corresponding increase in time, and auricular contractions would therefore be of significant importance even at comparatively slower heart rates.   This factor would make the occurrence of presystolic murmurs more likely in patent ductus arteriosus than the other instances of dilated left ventricle associated with diastolic murmurs.

SUMMARY

Apical diastolic murmurs similar to those heard in mitral stenosis were found in nine of 21 patients with patent ductus arteriosus. Five of these nine patients were operated upon. One patient died following operation and a normal mitral valve was found. In three patients the apical diastolic murmurs disappeared following ligation. In one patient the apical diastolic murmur persisted unchanged, although the diastolic murmur at the base disappeared. This patient was assumed to have a rheumatic mitral stenosis in addition to a patent ductus arteriosus.

A comparison of associated findings in the groups of patients with and without apical diastolic murmurs indicates that when these murmurs are found they can be added to other evidences (symptoms of cardiac embarrassment, poor nutrition, wide pulse pressure, accentuated pulmonic second sound, enlarged pulmonary artery with increased pulsation, and enlargement of the left heart) which indicate that the shunt from the aorta to the pulmonary artery is marked and that the patient is adjusting poorly.

It is suggested that three factors play a part in the production of the apical diastolic murmurs: enlargement of the left ventricular cavity; increased speed of blood flow through the mitral valve; and an increased tendency in children for the flow of blood into the ventricles during diastole to produce sound.

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THE USE OF BAL IN THE TREATMENT OF SKIN REACTIONS DUE TO GOLD THERAPY *

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BAL, 2-3-dimercaptopropanol or dithiopropanol, has recently been found effective in the therapy of some toxic reactions due to gold.[1, 2, 3, 4, 5] The use of gold in the treatment of rheumatoid arthritis has been advocated by many authorities, some of whom have stated that it is the most effective single therapeutic agent available.[6] Others have expressed the opinion that it is of questionable value.[7] Because of its toxic reactions, many internists have limited the use of the drug to the severe cases of rheumatoid arthritis which have failed to respond to other types of therapy. There has been a tendency in the past few years to reduce both the individual and total gold salt dosage.[8] Results have been almost as good with administration of the smaller amounts, while toxic reactions have been reduced. These toxic reactions to gold have occurred during the course of treatment or several weeks after completion of treatment, and have frequently persisted for many months. Previously, the accepted therapy for such reactions consisted of discontinuance of gold administration, initiation of supportive measures, including blood transfusions, and use of symptomatic treatment. BAL is of value in controlling certain toxic reactions, but its administration may have to be extended over a considerable period of time.

BAL was found by Peters, Stocken and Thompson[9] to afford protection against arsenical gases, such as Lewisite. These investigators utilized available information which indicated that arsenic had a strong affinity for the thiol or $-SH$ groups of the tissues. Eagle et al.[10] have reviewed the work of Walker, Rosenthal, Stocken and Thompson, who showed that combination of arsenicals with tissue proteins resulted in a disappearance of the reactive thiol groups of the tissue proteins. Stocken and Thompson[9] also found that certain dithiols were much more effective in binding arsenic than were the monothiols. Dithiopropanol (BAL) proved the most useful.

Several groups of investigators evaluated various preparations of BAL for local and parenteral administration.[11, 12, 13] They found the most stable and effective preparation for intramuscular use was one containing 10 per cent BAL and 20 per cent benzyl benzoate in peanut oil. The dosage of BAL recommended by Eagle,[13] on the basis of all available data, was that of 3 mg. per kg. body weight every four hours on the first and second days, four times daily on the third day, and two times daily on the fourth to fourteenth day, for the treatment of severe complications; and 2.5 mg. per kg. body weight four times daily the first and second days, two times daily

the third day, and one or two times daily on the fourth to fourteenth day, or until symptoms or findings disappear, for the treatment of mild complications.

Sulzberger and Baer [14] summarized the pharmacologic studies as follows: "Pharmacological studies in human beings have shown that side effects barely begin at the 2.5 to 3.0 mg. per kilogram level when four injections of this dose are given at four hour intervals on two successive days. The incidence of side effects increases rapidly when the dose is raised to 4 and 5 mg. per kilogram. All the side effects observed even at the higher dosage levels have been of a temporary nature. They included nausea, vomiting, headache, burning sensation of the lips, mouth, throat and eyes, pain in the teeth, lacrimation and salivation, muscular aches, burning and tingling of the extremities, feeling of constriction of throat and chest and elevation of systolic and diastolic blood pressure. These side effects usually are at their maximum at fifteen to twenty minutes after intramuscular administration of the BAL preparations." Obviously BAL should not be used unless really needed, since it is not innocuous. It is toxic and also has definite sensitizing properties.

The action of BAL in gold toxicity states is probably similar to its action in other heavy metal poisoning. The accepted hypothesis is that heavy metals, arsenic, mercury and gold exert their toxic effects by combination with the sulfhydryl groups of the activating protein of cellular enzyme systems to form stable compounds, thus inactivating these systems. [1] The sulfhydryl groups in BAL have a greater affinity for the metal, removing it from the protein-metal combination and thus restoring the normal enzyme system activity. The mobilized nontoxic metal and BAL compound is then excreted in the urine. The above reaction is reversible in most cases but apparently after a certain period of time becomes irreversible, in which case BAL is ineffective.

Cohen, Goldman and Dubbs [1] reported five patients with dermatitis following gold therapy treated successfully with BAL. Ragan and Boots, [2] in the same publication, reported on five patients, one with stomatitis and dermatitis and four with dermatitis following treatment with gold. Only two showed distinct improvement, whereas two showed only slight amelioration of long standing exfoliative dermatitis which followed large doses of a slowly absorbed gold preparation. There was no improvement in the remaining patient who had received the same preparation. Rundle [4] reported one patient who developed exfoliative dermatitis following gold therapy. She was successfully treated with BAL. Lockie, Norcross and George [3] reported the successful treatment with BAL of a patient with thrombocytopenia and a patient with agranulocytosis, both attributed to gold therapy. FitzPatrick and Schwartz [15] reviewed the literature and added two cases of aplastic anemia to the 18 previously reported following gold therapy. One of their cases received BAL but failed to recover. Recently Macleod [16] reported 15 cases of gold toxicity treated with BAL; 11 of these patients

had dermatitis; one had a stomatitis only; two had acute hepatitis, and one had hypoplastic anemia. BAL was used over a period of several days. The dermatitis was reported as improved following therapy but apparently persisted in practically all patients for several weeks to several months.

Freyberg, Block, and Levey [17] found that soon after gold was administered parenterally the plasma level rose and then gradually decreased as the metal was deposited in the tissues and excreted in the urine. An equilibrium was established between the tissues and the plasma, while the excretion of gold by the kidney was reduced as the plasma level fell. This process was repeated after each injection with the gradual accumulation of gold in the body and a gradual increase of gold in the plasma. When a significant amount of gold was given it was found in the urine for months, since excretion was slow. Ragan and Boots [2] have shown that gold excretion in the urine is markedly increased after the administration of BAL. They carried out preliminary studies on rats prior to using BAL for treatment of gold toxicity in humans. In view of the known facts concerning the metabolism of gold, it would seem that the administration of BAL over a period of time, with mobilization and excretion of gold in the urine, leads to "degolding" of the body, with reactivation of the affected enzyme systems and improvement of the patient's symptoms and findings.

The following two cases of dermatitis following gold administration treated with BAL are reported in detail since the total number in the literature is relatively small. The dermatitis in both responded to BAL therapy. The first patient developed a transient toxic reaction to BAL which did not recur after reduction of the dosage. The second patient became sensitized to BAL and developed a rather severe erythema and edema of the skin which lasted for several hours after administration of the drug. This sensitivity fortunately developed late in the course of treatment so the reaction was observed only after the last two injections of BAL.

CASE REPORTS

Case 1. A 64 year old white woman was first seen in consultation on April 29, 1947, because of a severe dermatitis attributed to gold therapy. She had received 285 mg. of gold sodium thiosulfate between October, 1946, and April, 1947, for an "arthritis" of the back and left shoulder of seven years' duration. During the entire course of chrysotherapy she had noticed itching of the skin and irritation of the conjunctiva, but the significance of these complaints was not appreciated by her physician. Early in April, 1947, approximately three weeks prior to my initial examination, she noticed intense itching and redness localized to the sole of the left foot. Within a few days this dermatitis involved both feet and the ankles, hands, and forearms. The involved skin began to ooze profusely. The lesions gradually extended to involve the entire trunk, neck, thighs, and arms. The skin of the face became red but no weeping lesions developed. There was itching and redness of the conjunctiva with profuse lacrimation. About this time she also noticed gross hematuria which lasted a few days. About two weeks after the initial skin lesions appeared, and a few days before hospitalization, she noted desquamation of the involved areas. She had received various local treatments with no improvement of the skin condition. A

diagnosis of exfoliative dermatitis due to gold therapy was made and hospitalization for treatment with BAL was recommended.

She was admitted to the hospital the following day, April 30, 1947. The blood pressure was 124/70 mm. Hg; the pulse rate was 88; the respiratory rate was 20, and the temperature 99° F. The significant finding consisted of an extensive exfoliative dermatitis involving the hands, forearms, arms, neck, chest, abdomen, back, thighs, legs, and feet. The hands and feet showed deep fissuring between the fingers and toes and on the palms and soles. The conjunctivae were injected.

The hemoglobin determination, red blood cell count, white blood cell count, and differential white blood cell count were normal. The platelet count was 144,000 per cu. mm. The urine was normal. There was no gross or microscopic hematuria.

The patient weighed 140 pounds, or 66 kg. The dosage of 3 mg. BAL per kg. body weight amounted to 198 mg. or approximately 2 c.c. of a 10 per cent solution. The dosage schedule recommended by Eagle was followed, 2 c.c. every four hours through the first two days, and four doses of 2 c.c. the third day. The patient at this time had little pruritus and there was striking improvement in the dermatitis. However, she complained of severe lacrimation and salivation with some pain in the extremities, so the individual dose of BAL solution was reduced to 1 c.c. and three injections per day were given for the next five days. At that time, after eight days of treatment, the fissures between the fingers and toes and the desquamated areas were healed. However, the skin remained erythematous and there was some itching. She was discharged from the hospital with instructions to return twice daily for 1 c.c. BAL intramuscularly. She received this dosage for the next three days. At that time, after 11 days of treatment, she was apparently well, so in view of the reported cases treated for only short periods the therapy was discontinued. Within two days there was a marked increase in the pruritus and erythema, so BAL therapy was resumed on a schedule of 1 c.c. twice daily for five days and then 1 c.c. daily for an additional four days. The response to the treatment was immediate and at the end of this period, 22 days after the start of treatment, the patient was asymptomatic,

TABLE I

Case 1

Number of Days Since Initiation of BAL Therapy	Dosage Schedule of BAL—c.c. of 10% Solution Intramuscularly	Amount of BAL Sol. Administered in Period (in c.c.)	Total Amt. Bal. Sol. Administered (cumulative)	Remarks—Status of Skin Lesions, Symptoms of Toxicity of BAL, etc.
1 to 3	2 c.c. every 4 hrs.	28	28	Marked improvement of the dermatitis. Cessation of pruritus. Marked lacrimation and pain in extremities due to BAL.
4 to 8	1 c.c. 3 times daily	16	44	Fissures and desquamated areas healed.
9 to 11	1 c.c. twice daily	16	50	Involved skin erythematous but no lesions present.
12 to 13	Omitted	—	—	Recurrence of pruritus and dermatitis.
14 to 18	1 c.c. twice daily	10	60	Cessation of pruritus and improvement of dermatitis.
19 to 22	1 c.c. daily	4	64	Complete healing of skin lesions.
23 to 26	Omitted	—	—	Recurrence of pruritus and dermatitis both palms and soles
27 to 29	1 c.c. twice daily	6	70	Improvement in dermatitis.
30 to 32	Omitted	—	—	Recurrence of dermatitis.
33 to 35	1 c.c. twice daily	6	76	Improvement in dermatitis.
36 to 38	1 c.c. daily	3	79	Complete healing of skin.
39 to 63	1 c.c. twice a week	7	86	No recurrence of dermatitis.
64th day	2 c.c.—single injection	2	88	No recurrence of dermatitis.
68th day	2 c.c.—single injection	2	90	Recurrence of dermatitis on palms and soles on July 10.
74th day	2 c.c.—single injection	2	92	Complete clearing by July 12. Recurrence dermatitis July 19.
84th day	2 c.c.—single injection	2	94	No recurrence of dermatitis.
93rd day	2 c.c.—single injection	2	96	No recurrence of dermatitis. Residual erythema at site of skin lesions.

though there was still some erythema of the previously involved areas. Therapy was omitted for four days. The dermatitis promptly recurred, with oozing of the skin of the extremities and fissuring of the skin between the fingers and toes. BAL was administered, 1 c.c. twice daily for the next three days, with marked improvement. Therapy was again omitted for a three day period, with an immediate flareup of the dermatitis. It was obvious that the "degolding" process took a considerable period, since about 30 days had elapsed since the start of the treatment. Therefore, it was decided to give sufficient BAL to control the dermatitis and continue treatment over several weeks, with gradually increasing intervals between injections. BAL, 1 c.c. twice daily, was given for three days and, with improvement, the dose was reduced to 1 c.c. daily for three days and finally to 1 c.c. twice weekly, with gradually lengthening intervals between doses. Dermatitis of the feet was used as an indication for the administration of BAL during the last month of therapy. Details of the dosage schedule are given in table 1.

This patient received a total of 96 c.c. of 10 per cent BAL solution containing 9.6 gm. of the drug over a period of three months. She developed minor toxic symptoms attributed to BAL, which disappeared and did not recur when the individual dose was reduced. Later the original dose was resumed without producing any toxic symptoms.

Case 2. A 50 year old male was admitted to the hospital on April 8, 1947, with a history of progressive rheumatoid arthritis of 15 years' duration. Physical examination showed a well nourished individual with multiple deformed joints. He weighed 155 pounds. His blood pressure, pulse rate, and temperature were normal. All the proximal interphalangeal finger joints were enlarged, and on the extensor surface of several of these joints were small nodules, several millimeters in diameter, some of which apparently contained fluid. The patient was unable to flex the fingers completely. The wrists were thickened. The right wrist was ankylosed and there was marked limitation of motion of the left wrist. The motions of the elbows and shoulders were only slightly restricted. There were typical rheumatoid nodules, about 1 cm. in diameter, just below the olecranon processes. The periarticular tissues and the synovia of the left knee joint were thickened. Extension of the left knee was limited to 150 degrees. There was also soft tissue thickening about both ankles. The hands were moist and there was erythema of the skin of the thenar and hypothenar eminences.

Blood examination was negative except for a sedimentation rate of 22 mm. per hour. The urine examination was negative. Serum uric acid, blood calcium, phosphorus, alkaline phosphatase, total nonprotein nitrogen, urea, creatinine, and plasma proteins were normal. Kidney and liver function tests gave normal results.

Roentgen-ray examination showed small punched out defects in the margins of several proximal interphalangeal finger joints, in the carpal bones, and in the lower ends of the ulna and radius bilaterally. The joint spaces between the carpal bones were markedly narrowed. Microscopic examination of tissue taken from a nodule and joint synovia showed the findings of rheumatoid arthritis. No evidence of gout was found in any sections.

In view of the long duration of the disease, the biopsy findings, and the failure to improve on conservative management, it was decided to treat this patient with gold sodium thiomalate. Between May 16, 1947, and August 12, 1947, he received 560 mg. of myochrysine intramuscularly. Late in July the patient complained of slight conjunctival irritation. On August 15 he developed a generalized rash, with polymorphous lesions of a slightly violaceous color. There was severe involvement of the skin of the hands with fissuring and desquamation. This dermatitis was considered

by Dr. James R. Webster as characteristic of the sensitization eruption described as atypical lichen planus reported during treatment with atabrine and gold.

Local therapy over a period of several days resulted in no improvement. On August 21, BAL therapy, 2 c.c. of 10 per cent solution intramuscularly every four hours, was initiated. This was continued for four full days, with marked improvement of the dermatitis. The following three days, 2 c.c. of BAL solution were administered every eight hours. At this time the lesions had almost completely disappeared, so for the next 10 days 1 c.c. of BAL solution was given twice daily. For the next week, 1 c.c. of BAL solution was given once daily. Since there was little evidence of dermatitis, 1 c.c. BAL solution was administered every second or third day. On September 26, four days after an injection of BAL, the dermatitis became severe, apparently because of inadequate therapy. Return to a dosage schedule of 1 c.c. BAL solution twice daily for the next week resulted in complete subsidence of the dermatitis. The dose was then reduced to 1 c.c. daily for five days and then 1 c.c. twice weekly for three doses.

TABLE II

Case 2

Number of Days Since Initiation of BAL Therapy	Intramuscular Dosage Schedule of BAL—c.c. of 10% Solution	Amt. of BAL Sol. Administered in Period (in c.c.)	Total Amt. Bal. Sol. Administered (cumulative)	Remarks—Status of Skin Lesions Symptoms of Toxicity of BAL, etc.
1 to 4	2 c.c. every 4 hrs.	48	48	Marked decrease in pruritus and improvement in dermatitis.
5 to 7	2 c.c. three times daily	18	66	Almost complete healing.
8 to 17	1 c.c. twice daily	20	86	Complete control of dermatitis.
18 to 24	1 c.c. daily	7	93	Complete control of dermatitis.
25 to 36	1 c.c. every second or third day	4	97	Recurrence of dermatitis.
37 to 43	1 c.c. twice daily	14	111	Complete healing of dermatitis.
44 to 48	1 c.c. daily	5	116	Control of dermatitis—complete healing.
51st day	1 c.c. single injection	1	117	Complete healing.
54th day	1 c.c. single injection	1	118	Reaction to BAL—erythema and edema of skin of 8 hours' duration.
57th day	1 c.c. single injection	1	119	Identical reaction.

On October 16, after receiving BAL, the patient reported that after the previous treatment on October 13 he had noticed intense itching and redness of the skin appearing several hours after the injection and lasting about eight hours. About four hours after the injection of BAL on October 16, 1947, the patient developed intense pruritus and a diffuse erythema over most of the body, with brighter macular lesions or "blotches" with ill-defined borders and up to several centimeters in diameter over the trunk. This differed markedly from the original toxic "gold" dermatitis. The skin was much more erythematous and was also slightly edematous. There was no hemorrhage into the involved skin. There were no ulcerations or fissures. The itching was intense. There were no true "whealing" phenomena. These lesions remained for about eight hours and then subsided spontaneously and completely without any desquamation or residual findings. There were no pain in the extremities, conjunctival irritation, lacrimation, or increased salivation, paresthesias, headache, malaise, nausea, vomiting, apprehension, weakness, or other evidences of BAL toxicity. Since the gold dermatitis was minimal, BAL therapy was discontinued.

This patient received a total of 119 c.c. of 10 per cent BAL solution containing 11.9 gm. of the drug over a period of eight weeks, with prompt control of his dermatitis. However, as in Case 1, there was a recurrence of the dermatitis when BAL was omitted for a few days as the interval between injections was increased. This man eventually developed a skin sensitivity to BAL. The skin manifestations were entirely different from the original toxic "gold" dermatitis. The drug was discontinued since the gold dermatitis was minimal.

COMMENT

The results of treatment with BAL in these two cases of dermatitis due to gold were gratifying. The exfoliative dermatitis in the first case and the lichen planus-like dermatitis in the second case were severe. Since the removal of gold from the body (or "degolding" the patient) usually results in reactivation of rheumatoid arthritis, BAL should not be used unless really needed. It is interesting to note that in most of the reported cases BAL was given for only a short time and in total dosage of from 1.6 gm. to 5.3 gm. Cohen et al.[1] used 11.2 gm. in one case. The two cases reported here received 9.6 gm. and 11.9 gm. over a period of 12 weeks and eight weeks, respectively. Some of the patients previously reported did not respond to BAL therapy, although they received total amounts of the same order as the successfully treated patients.

Analysis of the previously published case reports and these two cases shows that pruritus is controlled within the first few days of the BAL regime. The dermatitis, although improved soon after the start of treatment, may be slow to heal. The interval between the onset of dermatitis and initiation of BAL therapy may prove to be significant. However, Margolis and Caplan[5] reported good results in the case of one patient in whom this interval was 435 days and poor results in another patient in whom this interval was only 28 days. Another patient, treated after an interval of 362 days, showed some improvement. All these patients had received large amounts of Lauron. Ragan and Boots[2] reported a treatment failure in a patient who first received BAL 95 days after the onset of the rash. A total of 3,300 mg. of BAL was administered. This patient had received 1,000 mg. of an unspecified gold compound containing 500 mg. of metallic gold. The interval between the onset of rash and initiation of BAL therapy in the remaining reported patients, so far as can be determined, was less than 60 days.

Dermatitis noted after any one of the first few injections of gold, while usually mild, may be very severe, but in any case usually lasts only a short time since the total amount of gold to be excreted is small. Therefore, BAL is seldom indicated in therapy of dermatitis occurring early in the course of treatment. There is no particular point during a course of gold at which one can tell whether a toxic reaction will occur. As previously mentioned, such reactions may come on at any time during or even weeks after completion of chrysotherapy. The more gold administered, the longer will be

the excretory, or "degolding," period. The rate of absorption from the tissues after administration and the rate and mode of excretion also vary with the type of gold preparation administered. It has been shown experimentally by Block, Buchanan and Freyburg [15] that colloidal gold is slowly absorbed and is excreted mainly in the feces, whereas crystalline gold salts are relatively rapidly absorbed and excreted almost entirely in the urine.

Prolonged treatment of a recurrent dermatitis was necessary in both cases reported here. This point is emphasized, since patients previously reported were treated over relatively short periods of time. Theoretically, the "degolding process," mobilization of gold from the tissues, and excretion of the nontoxic gold-BAL combination should be continued until the plasma level of gold reaches a level which no longer interferes with the enzyme system whose inactivation is supposedly responsible for the dermatitis. From available information it is believed that the greater the store of gold in the body, the longer the period of administration or the greater the total dosage of BAL needed for "degolding." Therefore, it is suggested that treatment with BAL be continued over a period of time before being discarded. A recurrence of the exfoliative dermatitis is an indication for resumption of treatment or increase in the amount of BAL administered. A smaller individual dose at longer intervals will frequently suffice to control the dermatitis. However, the smaller dose regime probably results in slower excretion of the stored gold. Any patient who develops toxic reactions necessitating the use of BAL should not be given gold in the future.

The sensitization of the skin to intramuscularly administered BAL should be considered. The dermatitis which appeared in Case 2 after the use of BAL was entirely different from the gold dermatitis, though the same area of the body was involved. There was a diffuse erythema with deeper red, ill-defined lesions of a macular nature. No wheals were noted, though itching was very marked. This erythema appeared about two hours after administration of BAL and disappeared spontaneously eight to 10 hours later. There was no subsequent desquamation.

This occurrence of an apparently different type of skin lesion after sensitization is of interest. While Sulzberger, Baer, and Kanoff [12] have observed positive patch tests after intramuscular injections of BAL, they have not reported the occurrence of generalized skin lesions even after intramuscular injections of BAL were repeated in patients who had given positive skin tests. These authors stated that the skin sensitivity produced by BAL applied locally was neither the classical eczematous contact type nor the urticarial type, but a different form of allergic response which consisted of erythema and edema of the skin. It was noted that skin sensitivity to BAL developed in a high percentage of cases when the drug was applied to skin areas burned or damaged with Lewisite. They point out that BAL is a sensitizing agent when used in individuals with normal skin, and that its sensitizing capacity is still greater when used in individuals with damaged skin.

The frequency of such a skin reaction following intramuscular injection of BAL has not been determined. Case 2 would appear to be quite typical of the unusual allergic type in which urticaria does not occur.

It might be mentioned that Tye and Siegel [19] have reported on the successful therapy of acute BAL toxicity with epinephrine hydrochloride. They were also able to prevent toxic reactions in two individuals sensitive to BAL by the prophylactic administration of 25 to 50 mg. of ephedrine sulfate.

SUMMARY

1. Two patients with severe exfoliative dermatitis due to gold salts were successfully treated with BAL. One patient developed a toxic reaction to BAL and the other developed skin sensitivity to BAL.

2. The pruritus was relieved after the first few injections of BAL and the dermatitis improved within a few days. However, the use of BAL over extended periods (eight and 12 weeks) was necessary to control recurrences of dermatitis.

3. Individuals who have received considerable quantities of gold should be given BAL for several weeks, since the excretion of accumulated gold takes time. A recurrence of the dermatitis of the original type is an indication for the resumption of BAL treatment or for readjustment of the individual dose or the interval between injections.

4. BAL should not be administered for minor toxic reactions to gold since it is not an innocuous drug. A toxic reaction of sufficient severity to warrant the use of BAL should be a contraindication to further gold therapy.

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STATISTICAL STUDY OF 6,000 CASES OF DIABETES *

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INCIDENCE

THE incidence of diabetes in the total population is usually given as approximately 1 per cent. In reality, we do not know exactly what the incidence is. Gradually, however, we are getting more information. Data presented in this paper are derived from the records of 6,000 patients seen in the period from 1921 to 1948.

From 1921 to 1933, while I was at the Cleveland Clinic, I studied carefully the incidence of diabetes among all patients admitted to this institution (figure 1). During the last seven years of this period, the percentage of diabetics in this large group of admissions increased to between 3 and 4.75 per cent. This increase in the percentage of diabetic patients during these years reflected the fact that during that period blood sugar determinations were made routinely with the idea of uncovering hidden cases. This test had not been a part of the routine examination during the earlier years. These figures do not tell the incidence of diabetes in the general population, but merely represent the incidence of this disease in a large group of persons seeking medical attention for all types of illness. The point in question here is that if we look for diabetes and check all patients routinely, we will find it frequently in patients not suspected of having it, as was found in the Oxford investigation.[1]

The rule that I have followed in searching for diabetes has been as follows: If the fasting or the two and a half or more hours' postprandial blood sugar was elevated above the normal, such a case was worked out further from the standpoint of diabetes. The blood sugar at these two points should be normal. If it is not, it always calls for a further study of the patient. If the blood sugar is elevated one hour after a meal, it is of very little significance. The important point is: how long after a meal does it stay elevated; if more than two and a half hours, then the case is considered as one having diabetes.

In the data presented in figure 1 there may be another factor involved in producing the high incidence of diabetes, namely, the discovery of insulin which led many patients with diabetes to seek help from this new medicament. The fact remains, however, that if you look for diabetes systematically, you will find it much more frequently than if you wait until it becomes a "shoemaker diagnosis."

AGE

The incidence of diabetes according to age decades is represented in table 1. The ages given here are ages at the onset of diabetes, not at the time the patients were first seen by me. This shows virtually the same relative percentages as appear in my former publications,[2] which treated of smaller series. Table 2 shows comparative data of nine authors on the incidence of diabetes by decades.

Diabetes during the first year of life is usually regarded as exceptional, yet in this series there were 10 cases in the first and 14 in the second year of
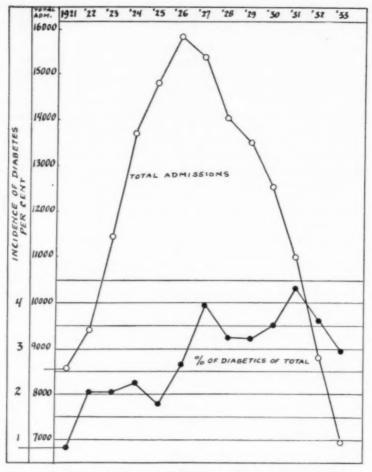
Fig. 1. Incidence of diabetes in total admissions at Cleveland Clinic, 1921-1933.

TABLE I

Incidence of Diabetes According to Decades

Decade	Cases	Per Cent
I	270	4.5
II	250	4.16
III	368	6.14
IV	708	11.8
V	1,397	23.28
VI	1,600	26.67
VII, VIII and IX	1,407	23.45
Total	6,000	

TABLE II

Incidence of Diabetes According to Decades
(Compiled from the Literature)

Author	Age Decades—Per Cent							
	I	II	III	IV	V	VI	VII	VIII
Frerichs	1.0	7.0	10.0	18.0	25.0	26.0	11.0	1.0
Seegan	0.5	3.0	16.0	16.0	24.0	30.0	10.0	0.5
Grube		1.7	2.8	11.2	23.1	39.5	18.1	3.4
Schmitz	0.83	4.1	9.3	17.3	22.3	32.6	10.0	3.3
Pavy	0.58	4.19	7.13	16.4	24.9	30.7	13.4	2.5
Kulz	1.0	3.0	4.6	17.2	36.0	26.8	9.2	0.1
von Noorden	1.43	1.43	4.2	9.78	16.7	14.3	3.0	0.4
John (present series)	4.5	4.16	6.14	11.8	23.28	26.67	23.45*	
Joslin (9853 cases)	4.7	6.8	7.82	12.29	23.14	27.32	18.0 *	

* VII, VIII and IX decade.

life.   Two of these cases, in fact, developed diabetes before they were a year old.

The contrast in age distribution of diabetic patients and of the general population is shown in figure 2.   One-third of the population is found in the first two decades of life, but only 7.2 per cent of all diabetics are under
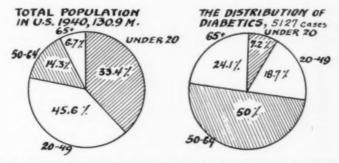
FIG. 2.   Comparative percentile age distribution of diabetics and general population.
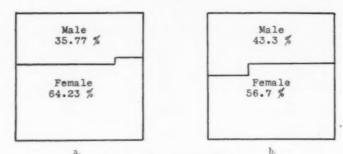
FIG. 3. Sex incidence of diabetes.
a. 6,000 diabetics of this series.
b. 9,182 diabetics, National Health Survey, 1935-36.

20 years. . Almost half the population, and 18.7 per cent of people with diabetes, are found in the third and fourth decades. Those in the sixth and the first half of the seventh decade comprise but 14.3 per cent of the population, but constitute 50 per cent of the diabetics. That is, one half of all diabetics are aged 50 to 65 years. Only 6.7 per cent of the population is over 65 years, but 24.1 per cent of diabetics are found in this advanced age period. Thus, 21 per cent of the general population is over 50 years of age, but 74.1 per cent of diabetics are in this group.

SEX

In this series, 43.3 per cent of the patients were male and 56.7 per cent female, thus confirming the fact that diabetes occurs more frequently in women, as reported by other workers (figure 3).

TABLE III

Fasting Blood Sugar on Admission, 5,589 Cases			Glycosuria on Admission at Various Blood Sugar Levels, 5,666 Cases				
Blood Sugar	Number Cases	Per Cent	Glycosuria No. Cases	Per Cent	No Glycos. No. Cases	Per Cent
120 or less	615	10.9	274	4.8	360	6.3
121–150	1,561	27.8	240	4.2	1,114	19.6
151–200	1,312	23.3	672	11.8	732	12.9
201–250	706	12.5	576	10.1	155	2.7
251–300	540	9.6	563	9.9	37	0.6
301–350	358	6.3	396	6.9	12	0.2
351–400	215	3.8	226	3.9	4	0.06
401–450	112	1.9	96	1.6		
451–500	71	1.2	95	1.6	1	0.01
501–600	66	1.2	110	1.9	1	0.01
601–700	18	0.3	2	0.03		
701–800	9	0.1				
801–900	5	0.08				
901–1000	1	0.01				

BLOOD SUGAR ON ADMISSION, WITH AND WITHOUT GLYCOSURIA

While the fasting blood sugar is no criterion for or against the diagnosis of diabetes unless it is high, it does offer some interesting information in a large series of new patients in showing the proportion of diabetic patients seen with various levels of blood sugar (table 3). A preponderant majority of patients, when first examined, show a blood sugar level of less than 250 mg. per cent. However, 24.4 per cent come with fasting blood sugar above 250 and, in some, the very high level of 900 to 1,000 mg. per cent is reached.

Table 3 also shows the percentage of patients exhibiting glycosuria at various levels of the blood sugar. Glycosuria can occur at any blood sugar level, from 60 to 1,000 mg. per cent, and hence is of little significance in determining the presence or absence of diabetes. However, table 3 shows a fact of considerable significance that is not always recognized, that is, that glycosuria cannot be predicted absolutely at any particular blood sugar level. The old teaching, that the renal threshold for sugar is at 180 mg. per cent, certainly is not sustained in these observations. While the renal threshold is at 200 or below in a large percentage of cases, a renal threshold above 200 mg. per cent was observed in 151 cases, or 8.2 per cent of this series. This fact indicates the need for revision of the old concept that a renal threshold above 180 mg. per cent is extremely rare.

The other interesting point which table 3 brings out is that many patients show glycosuria at a low blood sugar level. Thus, 274 cases, or 4.8 per cent, showed glycosuria at a blood sugar level of 120 mg. per cent or less. These are the cases which certainly cannot have the insulin dosage adjusted on the basis of glycosuria. I have seen many sad instances of this kind.

HEREDITY

That heredity plays a part in the incidence of diabetes has been shown repeatedly. Hansen,[3] for instance, considers diabetes an hereditary condition. He believes that most cases are isolated because the origin of symptoms depends upon a coincidence of disturbances rather than upon a single factor; he illustrates this by a series of genealogic tables.

Table 4 shows my own findings. The incidence of hereditary and familial diabetes in this group was 19.13 per cent, a figure much too high

TABLE IV

Heredity in Diabetes
(6,000 Cases)

Hereditary	Familial	Total
11.83%	7.3%	19.13%

Husband or wife—27 Cases
Son or daughter —17 Cases
Grandchild — 1 Case
Nephew — 1 Case

TABLE V

Heredity in Diabetes
(Reports from the Literature)

Author	Date	Cases	Familial or Hereditary Diabetes Per Cent
Grube			8.0
Frerichs		400	9.8
Seegen			14.0
Escudero	1933		16.0
Naunyn	1905	398	17.0
John (present series)	1948	6,000	19.13
Schmitz			20.0
Palmer	1929	300	20.0
Joslin	1923	2,800	21.0
Kulz		692	21.6
Williamson		500 ·	22.0
Bouchard			25.0
Umber			25.0
von Noorden	1917		25.4
Seckel	1925		26.0
Labbé	1931		27.5
Steiner	1936		35.1
Cammidge	1934		39.6
Hoogslag	1922		43.0

to be dismissed as coincidence.   This is the percentage for the total group, including all ages.

Experience suggests that the influence of heredity is actually larger than that indicated by the percentage figures.   This is because, at the time we first see the patient, the whole story of heredity often is not available.   Often I have seen a diabetic child whose history on admission was negative for diabetes in the family but whose father became diabetic months or years later.   Joslin has also stressed this point, and it behooves us to give more consideration to this factor than heretofore.

TABLE VI

Heredity in Diabetes in Children
(500 Children—Aged 1–19)

	Number Cases	Per Cent
Hereditary history of diabetes	116	27.1
Familial history of diabetes	19	4.4
No history obtained in	73	
Total		31.5

Hereditary history of diabetes:
    in Gentile children   26.4 per cent
    in Jewish children   33.3 per cent

Familial history of diabetes:
    in Gentile children   4.9 per cent
    in Jewish children   2.2 per cent

Total: Gentile 31.3, Jewish 35.5 per cent.

TABLE VII

Heredity in Diabetes
Jewish and Gentile Children
(From Literature)

Author	Cases	Per Cent	
		Gentile	Jewish
White	533		44.0
Priesel-Wagner	108	21.0	43.0
Ladd	35		37.0
Collens and Grazel	10		50.0
Lion and Moreau	100		23.0
Toverud	47		17.0
Holt	50		30.0
Landabure	60		41.6
Grishaw et al.	341		32.2
John	500	31.3	35.5

TABLE VIII

Standard Weight According to Age or Height

	Age	Height	Male	Female
Children	1		21	21
	2		27	27
	3		32	32
	4		36	36
	5		41	41
	6		46	44.4
	7		50.7	49.4
	8		55.4	53.5
	9		64.0	59.7
	10		67.1	66.1
	11		75.9	75.2
	12		81.3	80.7
	13		92.6	97.3
	14		103.6	105.6
Adults		4'8"		112
		4'9"		114
		4'10"		116
		4'11"		118
		5'	126	120
		5'1"	128	122
		5'2"	130	124
		5'3"	133	127
		5'4"	136	131
		5'5"	140	134
		5'6"	144	138
		5'7"	148	142
		5'8"	154	146
		5'9"	159	150
		5'10"	165	154
		5'11"	170	157
		6'	176	161
		6'1"	181	
		6'2"	187	
		6'3"	192	
		6'4"	198	
		6'5"	203	

Table 5 shows comparative findings on heredity published by various authors. There is considerable variation in these reports, but it must be realized that many of them are of early date.

In table 6 are shown the figures on heredity for young diabetics in my series, that is, patients in the first two decades of life. This demonstrates that in youth the factor of heredity is more important than in older patients. Table 7 also presents data on heredity in Gentile and Jewish children, gathered from the literature. Unfortunately, many authors have presented statistics on heredity only in Jewish children, but have not given figures pertaining to Gentile children for comparison. However, the fact that the hereditary factor is definitely higher in the Jewish group than among Gentile children is well established.

OBESITY

A study of weight in relation to diabetes presents some interesting information. Here the important fact to know is the highest weight ever reached by the patient, for this tells the true story in relation to obesity. The weight at the time of first observation is not a reliable criterion, because the patient may have lost 40 to 80 pounds as the result of undiagnosed diabetes. The important thing is whether he *was* at any time obese, and thus consuming larger quantities of food than necessary for his expenditure of energy. The data reported are based and calculated on the standards shown in table 8. These are the standards used at the Cleveland Clinic right from the start to date. I do not recall from what standard text they were taken. However, I feel it important to give these standards so that any calculation in the future will have the basic data.

TABLE IX

Overweight in Diabetics*

(2,970 Cases)

Per Cent Overweight	Males		Females		Total
	Number	Per Cent	Number	Per Cent	
Normal or below	266	20.1	304	18.4	570
10	237	17.9	201	12.1	438
20	239	18.0	209	12.6	448
30	207	15.6	225	13.6	432
40	160	12.1	204	12.3	364
50	98	7.4	205	12.4	303
60	64	4.8	111	6.7	175
70	26	1.9	80	4.8	106
80	13	0.6	44	2.6	57
90	6	0.4	34	2.0	40
100	3	0.2	15	0.9	18
110	2	0.13	8	0.4	10
120			4	0.2	4
130			1	0.05	1
140			2	0.1	2
180			1	0.05	1
220			1	0.05	1
Total	1,321	47.87	1,649	52.13	2,970

* Highest weight before or at time of diabetes.

In a group of 2,970 patients (table 9) on whom data were available on maximum weight (47.87 per cent were males and 52.13 per cent females), 62 per cent of the males and 69.5 per cent of the females had been at some time 11 per cent or more overweight.   The degree of obesity is indicated by stating the overweight in terms of 10 per cent increases.   Only 38 per cent of the males and 30.5 per cent of the females were of normal weight or below throughout their lives.   Hence it can be stated that the majority of those who develop diabetes are or have been definitely overweight.

The correlation of overweight with the blood pressure at the time of the appearance of diabetes (figure 4) indicates that there is greater elevation of blood pressure with increased obesity in the majority of cases.
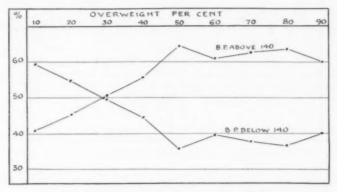
FIG. 4.   Correlation of blood pressure and obesity in diabetics.

Weight reduction, which means a low diet, definitely improves carbohydrate tolerance.   In the example shown (figure 5), the patient was an obese child, aged 13, who weighed 150 pounds.   The glucose tolerance test showed a diabetic curve.   On a diet of 1,400 calories her weight was reduced to 120 pounds and her carbohydrate tolerance improved immensely. A glucose tolerance test nearly a year after the first one was entirely normal. This patient, like others with similar histories, presented a question as to whether the diabetic condition, which was mild in 1934, was completely corrected, or whether it would be found that, "once a diabetic," she would be "always a diabetic."

The answer came in due time.   Her weight, owing to disregard of diet, again increased above 150 pounds in 1937 and the blood sugar began to rise. She married, had a miscarriage at three months in 1943, and in 1944 became a frank diabetic with a very high level of blood sugar which required insulin for its control.   It now appears likely that, to continue in good health, she will have to use insulin and watch her diet closely the rest of her days.
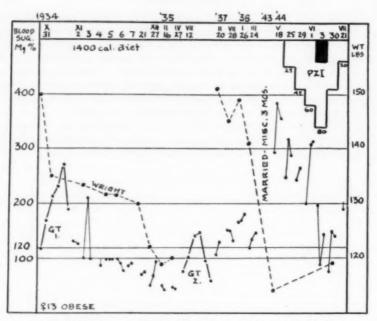
Fig. 5. Illustrative case showing effect of overweight on glycemic level.

Observation of numerous cases of this type has convinced me that hyperglycemia in the obese leads to frank diabetes if it is not counteracted by dietary restriction and weight loss.   Physicians should not be misled by contrary teachings that hyperglycemia in the obese is not diabetes but just a temporary disturbance of the carbohydrate metabolism which can be disregarded.

INFECTION

That infection plays a part in the etiology of diabetes has been disputed by some authors.   However, I have been convinced for many years that it is a definite factor in the production of diabetes in a certain proportion of cases.   The unknown factor in this problem, I believe, is that we know nothing of the physiologic-pathologic background in these patients, young and old, in whom diabetes develops following an infection; that is, whether there was a predisposition (the "Anlage" of the German authors) toward diabetes so that only those in whom there was such a weakness develop diabetes following an infection or repeated infections.   This is a problem for future research, and will take decades to solve.   It certainly offers a fertile field for investigation.

TABLE X

Onset of Diabetes in Children Following Infections

Infection	Time of Discovery of Diabetes Following Infection								Total
	1-10 Days	11-20 Days	21-30 Days	31-40 Days	41-50 Days	51-60 Days	1 Year	Not Stated	
Mumps	5	1	2			1	3	25	37
Influenza	9	7	7	2		5		3	33
Measles	2	1	2	1		1	2	2	11
Dysentery	1	1	1					3	6
Pneumonia			4		1		3	2	10
Intestinal toxemia								3	3
Boils	1	1	1						3
Tonsillitis	1	1		1		1			4
Nephritis								2	2
Glandular fever			2		1				3
Jaundice	2	1							3
Septic endocarditis								1	1
Poliomyelitis			1				1		2
Abscessed teeth				1					1
Infectious diseases								23	23
Pyelitis		1						1	2
German measles	1								1
Scarlet fever	2	1	1					1	5
Mastoiditis			1					1	2
Whooping cough			1	1		1	1		4
Chickenpox	2		2						4
Infection	1	1	1						3
Otitis media			1						1
Total	27	16	27	6	2	9	10	67	164

Here I am presenting my data only on children in whom diabetes developed within a year following an infection, usually one of the acute exanthemata. Table 10 shows that 70 children developed diabetes within a month and 27 within 10 days following an infection. Actually, the number is higher than that, for the time between the infection and onset of diabetes was not stated in a large proportion of the records (67 of 164 cases). These

TABLE XI

Deaths in 6,000 Diabetic Patients
(1920-1948)

Decade	Diabetic Coma	Insulin Shock	Other Diseases	Suicide	Accident	Unknown Cause	Total	Per Cent
I	9	1	5		2	2	17	2.66
II	13		6		2		21	3.28
III	9		11	1		1	22	3.44
IV	7		14	1		1	23	3.59
V	16		51	1		11	79	12.36
VI	14		127	1	2	16	160	25.03
VII	10		175		2	13	200	31.29
VIII	3		82		1	7	93	14.55
IX			24				24	3.75
Total	81	1	493	4	9	51	639	
Per Cent	12.6	0.15	77.1	0.6	1.35	7.98		
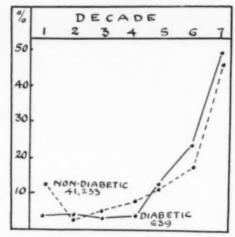
Fig. 6. Comparison of age at death of diabetics and non-diabetics.

figures certainly suggest that the infection had something to do with the onset of diabetes in these cases, and the burden of proof against this reasoning falls on those who say it did not.   I believe that, if we had more extensive data on diabetic children from all over the country, these would be quite revealing of the rôle of infection in precipitating diabetic symptoms.

Similar observations in regard to infection are also common in adults. Diabetes often is revealed shortly after pneumonia, gall bladder infection, influenza, cystitis or pyelitis.   Diabetes also occurs frequently in patients with severe hyperthyroidism, in which ketosis blocks the action of insulin (endogenous), thus producing hyperglycemia.   If this is allowed to continue, permanent diabetes results.

For all these reasons it is difficult for me to disregard infection as an etiologic factor in diabetes.   Time, I believe, will bring forth further evidence to substantiate this relationship.

SYPHILIS

That there is an etiologic relationship of significance between syphilis and diabetes, as believed by some European writers, has not been borne out in studies of large groups of cases observed since the advent of insulin. Actually, syphilis is a relatively rare complication of diabetes and its incidence among people with diabetes is apparently lower than in the general population.   In the present series of 6,000 cases, syphilis was present in 1.88 per cent.   This corresponds almost exactly to Joslin's figures of 1.9 per cent in 5,086 cases of diabetes.   Most authors who have reported a high incidence of syphilis among patients with diabetes have been Europeans, and such reports are usually based on a relatively small number of cases.

MORTALITY

The present study covers a period of 27 years, from March 1, 1921, to December 31, 1947. Thus it includes some cases seen in the pre-insulin era, when treatment of diabetic coma or serious infections of the lower extremities was practically hopeless. My figures on mortality are derived solely from cases in which I have a record of death. They do not by any means include all deaths in the 6,000 cases. But even so, I felt that data on 639 deaths should be of value.

The pertinent questions regarding the mortality in a large series of cases are:


```
                    NUMBER   OF  CASES
  10 20 30 40   60    80       120       160       200      240
=============================Diabetic coma        Cardiorenal
=======================Post-operative, includes oper.for gangrene.
==================Pneumonia
================Carcinoma
=============Tuberculosis,pulm.
=========Septicemia
========Embolism, infarcts.
======Accidents
=====Hyperthyroidism,crisis.
====Suicide.
====Cirrhosis of liver.
===Carbuncle.
===Gen.peritonitis.
===Otitis media.
==Infection.
==Erysipelas.
==Christian science. Coma.
==Ruptured appendix.
==Infectious parotitis.
=Hemorrhage. Prim.& secondary.
=Convulsions.
=Lung abscess.
=Pernicious anemia.
=Ptomain poisoning.
=Purulent endocarditis.
=Cerebellar tumor.
=Skull fracture.
=Meningitis.
=Insulin shock.
=Alcoholic coma.
=Chronic ergotamine poisoning.
=Acute leukemia.
==========Unknown.
                              CAUSES OF DEATH IN DIABETICS 639
```

FIG. 7. Causes of death in 639 patients with diabetes.

1. At what age do people with diabetes die?
2. How does the age at death compare with that from other causes?
3. What is the most frequent cause of death in people with diabetes?
4. How long was diabetes present before death?

TABLE XII

Duration of Diabetes According to Age When Diabetes Developed

Had Diabetes. Years	Diabetes Developed. Decade	Number of Cases
Under one year	1	1
	2	2
	3	3
	4	3
	5	18
	6	12
	7	11
	8	9
	9	1
1 to 5 years	1	40
	2	51
	3	5
	4	4
	5	12
	6	23
	7	28
	8	11
6 to 10 years	1	35
	2	52
	3	3
	4	3
	5	19
	6	37
	7	27
	8	6
11 to 15 years	1	11
	2	17
	3	1
	4	8
	5	19
	6	26
	7	13
	8	3
16 to 20 years	1	2
	2	1
	3	2
	4	7
	5	12
	6	13
	7	8
21 to 25 years	1	1
	3	2
	4	2
	5	9
	6	4
	7	3
26 to 30 years	3	1
	4	1
	5	1
	6	1
36 to 40 years	3	2

The answers to these questions as furnished by this series follow:

1. Of the 639 deaths which have been studied, the majority were in the sixth and seven decades (360 cases, or 56.33 per cent: table 11). The percentage of patients with diabetes who died after they reached their sixtieth year was 49.59, or approximately half. In this group, 93 reached the eighth and 24 the ninth decade of life.

2. The mortality curves of diabetics and non-diabetics resemble each other closely (figure 6). There is practically no difference in the two groups as to age distribution. The reason for this is quite obvious, since, with the exception of coma, deaths in diabetics are not due to diabetes, and hence should closely resemble those of non-diabetics from varied causes.

3. As noted above, diabetics usually die of something other than diabetes. Only in those who die in diabetic coma can diabetes be said to be the direct cause of death. However, diabetes is an aggravating factor in those who succumb to cardiorenal diseases (figure 7). Many diabetics develop arteriosclerosis, intercapillary glomerulosclerosis, retinal hemorrhages and detached retinas, accounting for part of the deaths grouped as of cardiorenal cause, which constituted the principal reason for death (239 cases, or 37.4 per cent). The rather high incidence of diabetic coma as the cause of death is attributable to the fact that the series contains cases antedating the use of insulin and, also, that some of these patients died in small communities where adequate hospital facilities were not available and the physician in charge was still unacquainted with the use of insulin in the early insulin era.

4. The duration of diabetes is shown in table 12. This varied from less than a year to 39 years. Correlation of the duration with the age at which diabetes developed shows considerable variability. This too is explained by the fact that the mortality in diabetics statistically does not reflect purely diabetic mortality in diabetics, but also all the other hazards and illnesses that afflict these patients, just as they do other persons. Two diabetics, one who has had the disease less than one year and the other for 20 to 30 years, may die of the same additional condition.

SUMMARY

1. An analysis of 6,000 cases of diabetes mellitus is presented.

2. The incidence of diabetes at large is not known precisely, but it is somewhere between 1 and 2 per cent of the population.

3. The incidence of diabetes in the first three decades is low. It starts to rise in the fourth decade, and from the fifth decade on it is the heaviest.

4. In this series of 6,000 cases of diabetes, 43.3 per cent were male and 56.7 per cent female.

5. Blood sugar on admission varied from less than 120 mg. per cent to 1,000 mg. per cent.

6. Glycosuria at a low blood sugar level (120 mg. per cent or less) was present in 360 cases, or 6.3 per cent. In these examinations the bladder was emptied on rising and the urine examined at 8 a.m. was thus passed about an hour after the discarded specimen.

7. The teaching that the renal threshold is at 180 mg. per cent of blood sugar concentration is not borne out by these studies. It can be found anywhere from 50 to 600 mg. per cent of blood sugar.

8. Heredity in the present series was found in 7.3 per cent of familial and in 11.83 per cent of hereditary. In children, on the other hand (first two decades), it was found in 31.5 per cent. It is slightly higher in the Jewish than in the Gentile children.

9. The majority of people who develop diabetes are or have been overweight. Sixty-two per cent of the males and 69 per cent of the females in this series had been at some time 11 per cent or more overweight.

10. Weight reduction improves carbohydrate tolerance. It does not "cure" the patient of his diabetes. The *anlage* is still there and is likely to flare up with an increase in weight or an intercurrent infection.

11. Infection does play a part in the etiology of diabetes. (See table 10.)

12. Syphilis plays but a small rôle in diabetes; in this series of 6,000 cases it was found in only 1.88 per cent.

13. The most frequent cause of death among diabetics, in the 639 deaths I have a record of was cardiorenal disease; next came diabetic coma; then postoperative deaths, which include operations for gangrene; and then pneumonia.

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TUBERCULOSIS IN STUDENT NURSES AND MEDI-
CAL STUDENTS AT THE UNIVERSITY OF
WISCONSIN *

By HELEN A. DICKIE, M.D., F.A.C.P., *Madison, Wisconsin*

IN the school year of 1933–34 a tuberculosis case-finding program was started in the Student Health Service of the University of Wisconsin. The problem of tuberculosis control among the medical students and student nurses was delegated to this department. With the complete coöperation of the Medical School and the School of Nursing we have been able to carry out the program as desired. With few exceptions, all students have been tuberculin tested on entrance to these schools. Since many of the students have their undergraduate college work at the University, we frequently have tuberculin records prior to their professional training. The program has been changed little in the case-finding method since its inception. All students are tested with .01 mg. O.T. and, if no reaction, with 1.0 mg. O.T. If no reaction is noted, the tuberculin negative individuals are retested at six month intervals. The tuberculin positive students are not retested unless the tuberculin reaction is questionable, i.e., edema or redness of less than 10 mm. Chest roentgenograms are repeated at six month intervals on all tuberculin reactors. Regardless of the reaction, roentgenograms are obtained on admission and graduation. On the Mantoux converters, chest roentgenograms are requested at more frequent intervals for the first year.

In October of 1942 we started using B.C.G. vaccination. Through the coöperation of Dr. S. R. Rosenthal, from the Tice Laboratory, we were able to secure the vaccine. He has continued to advise us in the perfection of his multiple puncture technic.

The B.C.G. vaccination is made available to all tuberculin negative students in the two professional groups who request it. We require a normal chest roentgenogram, no reaction to tuberculin with .01 mg. and 1.0 mg. O.T., and no known contact in the month before and the month following vaccination. For this reason the vaccination is done just prior to clinical contact, at the end of the first semester of the sophomore year in the Medical School, and at the end of the first semester of nurses' training. No control group has been maintained. The vaccination is neither required nor urged. Following the vaccination, all the students are tuberculin tested in one month and at six-month intervals thereafter. Chest roentgenograms are obtained as for the tuberculin positive group, i.e., every six months.

The opportunity for contact with tuberculosis is not as great as one would anticipate in a large general hospital admitting acutely ill patients.

Since 1944 the majority of the patients admitted to Wisconsin General Hospital have had routine photofluorograms. Both the student nurses and the medical students have a tuberculosis service. The medical students are assigned to the tuberculosis isolation ward for a few weeks in their sophomore year for physical diagnosis section work. In their senior year they have a two-week service at Wisconsin State Sanatorium and one week in the tuberculosis service at Wisconsin General Hospital. On both services, infectious disease technic is used. The student nurses have three weeks on the tuberculosis service at Wisconsin General Hospital. Eight weeks after completion of the tuberculosis service, the tuberculin negative student nurses are tested. This testing has not given any indication that the liability of infection on this service is greater than on other services.

In addition to the information available from their records as students, we have attempted to obtain adequate subsequent information by questionnaires. In a professional group we believe that such information can be accepted without serious question as to its reliability. In this questionnaire we requested information concerning the present tuberculin test if the individuals had been nonreactors at graduation, and a report on a recent 14 by 17 chest roentgenogram. If known, the approximate time of tuberculin conversion was to be recorded. If tuberculous disease had occurred, a complete report of the type and extent of the disease was obtained, as well as information concerning the bacteriologic studies, therapy, and present status. Several of the students who developed tuberculous disease had been examined by this department, and their entire series of roentgenograms was reviewed.

The response to the questionnaire was not as complete as we might have expected from a professional group. The failure of proper addresses during the immediate postwar period contributed in part. However, the response was regarded as adequate for the purpose of this report.
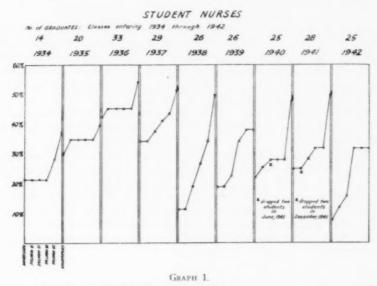
Because of the use of B.C.G vaccination, we have divided the graduates of the Medical School and School of Nursing into two groups, those having been graduated before B.C.G. vaccination and those having been graduated subsequent to the use of B.C.G. Among the Medical School graduates of the classes of 1934 through 1943, we have recent information on 283 of 545, or 59.2 per cent. In the graduates of 1944 through 1947 there were a total of 248. Adequate information is available on 196, or 79 per cent of these graduates.

Among the graduates of the School of Nursing prior to B.C.G. vaccination we have recent reports of 112 of 252, or 44.4 per cent of the graduates in the classes of 1934 through 1944. In the classes of 1945 and 1946 we have postgraduation information on 53 of 73, or 72.6 per cent of the graduates.

With few exceptions, we have complete records on the graduates who did not return the questionnaires, but we will not include them because of lack of adequate knowledge as to their present status. None of the students who had tuberculosis during their training was omitted.

In any study on tuberculosis occurring in a group with an occupational hazard, it is important to know the probability of tuberculous infection. There is no doubt that tuberculin sensitivity is the most reliable method of determining tuberculous infection.   The proper test dose of Old Tuberculin, or P.P.D., is still an unsettled problem, although there is considerable evidence that too large a test dose gives rise to a larger number of questionable reactions which are not constant.[1]   With the use of 1.0 mg. O.T. as the final testing dose, we may have included some individuals who actually were not infected but who showed only a nonspecific reaction.   In the past several years, all students with doubtful reactions have been retested and considerable variations have been noted in the reaction.

STUDENT NURSES

GRAPH 1.

Ordinate—Percentage of class tuberculin positive.
Abscissa—Time intervals entrance to graduation as indicated in the block.

The student nurses have shown rather wide variation in tuberculin sensitivity at the entrance to training, from 8 per cent to 42 per cent (graph 1 and table 3), but there has been no constant decline in tuberculin sensitivity.   Likewise, the tuberculin sensitivity has shown no significant variation at the completion of their period of training in the classes of 1934 to 1942.   The percentage of negative tuberculin students who became tuberculin positive during their training varied from 42 per cent among those entering in 1938 to 14 per cent in those entering in 1935.   There has been no decline noted in rate of conversion in the period prior to the use of B.C.G.

TABLE I

Medical Students: Tuberculin Sensitivity

	Class of 1940 48*		Class of 1941 49*		Class of 1942 44*		Class of 1943 61*		Class of 1943** 57*	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Pos. on entr.	12	25	16	33	13	30	14	23	15	26
Pos. 1st yr.	15	31	16	33	14	32	21	34	18	32
Pos. 2nd yr.	16	33	19	39	18	41	22	36	18	32
Pos. 3rd yr.	18	38	27	55	20	46	22	36	22	39
Pos. 4th yr.	20	42	33	65	24	54	36	59	24	42

* No. in class.
** Two classes in 1943.

Likewise, the medical students have shown no constant change in the tuberculin sensitivity level at the time of entrance or graduation (table 1 and table 2). The rise of tuberculin sensitivity level in the classes of 1944, 1945 and 1946 is the only major deviation, and this undoubtedly is attributed to the assignment of a large group of nonresident students under the Army and Navy training programs.

In both groups the degree of tuberculin sensitivity at the time of entrance to training is comparable to that of the University population of the same age and sex.

In determining the incidence of tuberculous disease in the tuberculin negative group it is essential that the rate be determined on those actually infected. The risk to the individual must be expressed in two ways: first, the liability of infection, and second, the liability of developing manifest disease if infected. The failure to estimate the incidence of tuberculosis only on the number actually infected gives rise to a deceptively low incidence among the original tuberculin negative students if the infection rate be low.

TABLE II

Medical Students: Tuberculin Sensitivity at Mid-Sophomore Year
Prior to B.C.G. Vaccination

	No. in Class	No. Tbn. Pos.	Per Cent Tbn. Pos.
Class of 1944	58	25	43
Class of 1945	78	32	41
Class of 1946	72	30	42
Class of 1947	72	21	29
Class of 1948	65	21	32
Class of 1949	50	11	22
Class of 1950	80	27	34
Earlier classes			
Class of 1934 (as seniors)			55
Class of 1937 (as freshmen)			45
Class of 1938 (as freshmen)			32

The incidence of tuberculosis in the groups included in this report has been consistently greater in the tuberculin converter than in the students who entered with a positive tuberculin test (table 4).   Among the graduates of the Medical School in the classes of 1934 to 1943, there are 19 of 188 original tuberculin negative students who developed tuberculosis.   If based on the

TABLE III

Student Nurses: Tuberculin Sensitivity on Entrance to Training
Prior to B.C.G. Vaccination

	No. in Class	No. Pos.	Per Cent
Entering 1943	49	12	25
Entering 1944	49	10	20
Entering 1945	41	4	10
Entering 1946	35	8	21
Entering 1947	39	5	13
Entering 1948	38	4	11

TABLE IV

Tuberculosis Developing in Medical Students and Student Nurses
Correlated with Their Original Tuberculin Status

MEDICAL STUDENTS: Classes of 1934 through 1943 (283 responses from 545 students)

	Total	Cases of Tuberculosis	
		No.	Per Cent
Original tuberculin positive	95	2	2.1
Original tuberculin negative	188	19	10.1
Tuberculin negative (1947)	50	0	
Tuberculin converters	138	19	13.7

MEDICAL STUDENTS: Classes of 1944 through 1947 (196 responses from 248 students)

	Total	Cases of Tuberculosis	
		No.	Per Cent
B.C.G. Vaccinated	106	1	0.95
Original tuberculin positive	46	2	4.3
Original tuberculin negative (not vaccinated)	44	6	13.6
Tuberculin negative (1947)	10	0	
Tuberculin converters (without B.C.G.)	34	6	17.6

STUDENT NURSES: Classes of 1934 through 1944 (112 responses from 252 students)

	Total	Cases of Tuberculosis	
		No.	Per Cent
Original tuberculin positive	33	1	3.0
Original tuberculin negative	89	8	8.9
Tuberculin negative (1947)	30	0	
Tuberculin converters	59	8	13.6

TABLE V

Student Nurses: Tuberculosis
Classes of 1934 through 1944

Name	Class	Entr. Tbn.	Grad. Tbn.	Subcu. Tbn.	
E. G.	1934	Neg.	Pos. Feb. 1932		June, 1932, moderate increase in hilum structures. Jan., 1933, right first interspace infiltrate and hilar thickening. No parenchymal disease. Bed rest at home with subsequent complete resolution. Chest roentgenograms now clear. No gastrics done.
R. M.	1940	Neg. Incl. Dec. 1937	Pos. May 1938		Small infiltrate right second interspace May, 1936. Gastrics positive by guinea pig inoculation in Sept., 1938. Slight increase in lesion by Dec., 1938, then clearing somewhat. By Dec., 1939, lesion noted at extreme apex in third interspace on right. Gastrics had been negative on three occasions since the positive in Sept., 1938. Patient entered sanatorium Nov., 1939. Right pneumothorax started. Completed nurses' training with pneumothorax. Now working. Chest roentgenograms reported stable. Length of pneumothorax treatment Dec., 1939, to 1941.
I. K.	1940	Neg. Incl. Dec. 1938	Pos. May 1939		Small infiltrate in left first anterior interspace peripherally May, 1939. Gastrics negative. Lesion gradually fibrosed and left several minute calcified areas. Recent roentgenograms show no change.
C. A.	1941	Neg. Incl. Jan. 1939	Pos. June 1939		Pleural type of pain started Dec. 23, 1939. On Jan. 27, 1940, pleurisy with effusion. Gastric and pleural fluid cultures negative. Rested at home Jan., 1940, to Sept., 1940. No parenchymal disease ever noted. Present chest roentgenogram reported normal.
G. G.	1941	Neg. Incl. Dec. 1939	Pos. May 1940		Roentgenogram of June, 1940, normal. Feb., 1941, small infiltrate noted in second left interspace. Gastrics negative. By Aug., 1941, the lesion had decreased. Chest roentgenogram now normal.

TABLE V—*Continued*

Name	Class	Entr. Tbn.	Grad. Tbn.	Subseq. Tbn.	
D. S.	1943	Pos.	Pos.		Bilateral apical caps with small subpleural infiltrates. Calcified complex on left. Gastrics positive Dec., 1941, by culture. Sanatorium care for four months. Gastrics negative. No change of any significant degree observed from her admission roentgenogram to the one at the time gastrics were checked. Recent chest roentgenogram shows persistence of lesion but gastrics are negative.
W. M.	1944	Neg. Incl. Sept. 1943	Pos. Nov. 1943		Roentgenogram of Nov., 1943, normal. In April, 1944, a 0.5 cm. infiltrate in periphery of third interspace noted. No change up to Jan., 1945. Recent roentgenogram in Army reported as normal. No gastrics done.
D. V.	1944	Neg. Incl. Nov. 1943	Pos. Jan. 1944		Jan. 27, 1944, chest roentgenogram negative. April, 1944, very questionable change in right second interspace. May, 1944, minimal infiltrate in periphery of right second interspace. Gastric aspirations positive. Sanatorium care with gradual clearing to June, 1945, and then acute spread after hemoptysis. Large right apical cavity and right upper lobe bronchitis. Thoracoplasty (seven ribs). Discharged March, 1947, with gastrics negative on several occasions by culture.
M. S.	1944	Neg. Incl. Sept. 1943	Pos. Nov. 1943		Nov., 1943, stringy infiltration in right first to third interspaces extending out from hilum. Gastric cultures positive. Bed rest at home for six months and then gradual increase of activity with return to training on reduced schedule. Gradual decrease in this disease process until chest appears normal at present time.

TABLE VI

Students with Hilar Adenopathy

Name	Sex	Class	Entr. Tbn.	Grad. Tbn.	Subseq. Tbn.	
H. L.	M	1935	Not known	Neg.	Pos. to avian tbn. only	Marked mediastinal lymphadenopathy, "hyperplastic tuberculosis," from cervical node biopsy. Bed rest six months with gradual clearing. Roentgenogram has been normal for 11 years.
G. A.	M	1936	Neg.	Neg.	Pos. 1939	Hilar adenopathy first observed Feb., 1940. Gastrics negative. Gradually cleared over period of two years. No recurrence since 1942.
O. O.	M	1942	Pos.	Pos.		Mediastinal lymphadenopathy March, 1944. Diagnosed as Hodgkin's. Roentgen therapy 1,500 r with gradual regression over period of 16 to 18 months. Tuberculin test became negative. Impression changed to Boeck's sarcoid. August, 1946, normal chest roentgenogram. Mantoux test again ++ with 1.0 mg. O.T.
H. B.	M	1943	Neg.	Neg.	Pos. 1945	April, 1942, left hilar adenopathy on routine roentgenogram. Tuberculin test repeatedly negative with 1.0 mg. O.T. Spleen palpable 3 cm. Biopsy of inguinal node "chronic lymphadenitis." March, 1943, chest roentgenogram had returned to normal. In January, 1945, inguinal node abscess developed. Positive for tubercle bacilli on culture. Axillary node reported "positive" on microscopic exam. Impression of tuberculosis of lymph nodes made at Bruns General Hospital. Now well. Chest roentgenograms have been normal.
F. G.	M	1943	Neg.	Neg.	Pos. 1946	Bilateral hilar adenopathy noted soon after tuberculin conversion. This was minimal in extent and gradually decreased to normal in six months. Chest roentgenogram normal Sept., 1947.
V. M.	F	1947	Neg.	B.C.G. Feb. 1943	Tbn. test remained pos. subsequent to B.C.G.	In May, 1947, routine roentgenogram showed distinct bilateral nodular thickening of the hilum shadows. Previous roentgenograms, including one in Sept., 1946, were normal. A-G ratio normal. Sputum negative for tubercle bacilli on culture. Axillary node biopsy showed chronic lymphadenitis. June, 1947, slight increase in nodular thickening on right. Impression: Probably sarcoidosis. Stable roentgenograms to Dec., 1947, without any treatment. Feels well and is completing internship.

TABLE VII

Medical Students: Tuberculosis
Classes of 1934 through 1943

Name	Sex	Class	Entr. Tbn.	Grad. Tbn.	Subseq. Tbn.	
W. W.	M	1935	Neg.	Neg. Incl. May 1936	Pos. Oct. 1936	Reports "primary infiltrate which gradually calcified." This appeared shortly after tuberculin conversion Oct., 1936. In June, 1935, negative chest roentgenogram. Nov., 1936, "organizing Ghon tubercle first recognized."
S. E.	M	1935	Neg.	Neg.	Pos. about one year prior to onset of disease	Chest roentgenogram normal May, 1936. In Feb., 1937, bilateral apical disease with 1 cm. cavity at right apex. Small nodular area at summit of right apex and a small wedge of density at the periphery of the first interspace laterally. Sputum negative. No gastrics at this time. Sanatorium care March, 1937, to Dec., 1937, bed rest only. Stable roentgenograms now for nine years with very little residual.
H. A.	M	1936	Neg.	Pos. 1935		In March, 1936, moderately advanced right apical tuberculosis (small cavity). Gastrics positive then. Sanatorium care 17 months, last 10 months part time work. Right pneumothorax six years. Roentgenograms stable for six years.
E. C.	F	1936	Neg.	Pos. Spring 1936		Previous roentgenograms negative. In June, 1936, minimal lesion right apex. Sanatorium care with bed rest July, 1936, to June, 1937. Sputum negative. Gastrics not done. Recent roentgenograms show little residual.
M. S.	M	1936	No record	No record	Not done	Minimal lesion at right apex discovered on internship. No gastrics or sputum studies. By 1942 the lesion had increased but no diagnostic work done. Then no further roentgen studies until May, 1947, following a frank hemoptysis. Roentgenograms then showed bilateral apical disease with marked increase since 1942. Sputum and gastric cultures were negative May, 1947.
R. D.	M	1937	Neg.	Pos. Nov. 1934		Chest roentgenograms normal, including one in June, 1938. In April, 1939, left infraclavicular disease with cavity found. No gastrics done and patient had no sputum. One year sanatorium care. Right pneumothorax 1939 to 1942. Stable lesion since then.
C. H.	M	1937	Neg.	Pos. Nov. 1934		Roentgenogram Nov., 1934, normal. Withdrew second semester. In May, 1935, symptoms of pneumonia. June, 1935, x-ray showed right upper lobe caseopneumonic disease with cavity. Sputum positive. Sanatorium care 1935 to 1937. Eight rib thoracoplasty. Gastrics negative and roentgenograms stable since 1937. Completed medical training in 1942.

TABLE VII—*Continued*

Name	Sex	Class	Entr. Tbn.	Grad. Tbn.	Subseq. Tbn.	
J. G.	M	1937	Neg.	Neg.	Pos. 1939	1939 chest roentgenogram negative. No further roentgen examinations until Sept., 1946, then bilateral first interspace fibrous appearing lesions noted. Six a.m. gastrics negative and roentgenograms show stable lesions since 1946.
H. V.	M	1938	Neg.	Neg.	Pos. May 1939	July, 1939, pleurisy with effusion. Sanatorium care. In May, 1940, developed miliary tuberculosis with tuberculous meningitis. Autopsy confirmed diagnosis.
R. S.	M	1938	Neg.	Neg.	Pos. July 1939	In July, 1939, "minimal lesion in left upper lung." No sanatorium care. This lesion gradually cleared over a period of three years. No gastrics done. Normal chest roentgenogram now.
R. P.	M	1938	Neg.	Neg.	Pos. 1940	Feb., 1942, bilateral apical disease with small cavity on right. Gastric aspirations positive by culture. Sanatorium care five months. Stability of minimal residual disease for four years.
N. G.	M	1939	Neg.	Pos. 1938		Sept., 1938, minimal infiltrates in both infraclavicular regions which showed increase in size. Sanatorium care for several months, then returned to school Feb., 1940. Subsequent increase in disease with return to sanatorium. Bilateral pneumothorax started after bed rest failed to convert sputum and gastrics. Finished medical training in 1943 with bilateral pneumothoraces. Reports roentgenogram stability over past two years (apparently has had pneumothorax treatment discontinued).
O. H.	M	1939	Neg.	Neg.	Pos. Sept. 1942. First pos. 1941	Acute pleural effusion of undetermined etiology Sept., 1942. Gastric aspirations and fluid cultures negative. In view of recent positive tuberculin test and no other etiological factor considered tuberculous in origin. Bed rest for six months.
M. M.	M	1940	Neg.	Pos. 1938		Chest roentgenograms normal 1938 and Dec., 1939. March, 1941, "bilateral apical infiltration." Three months sanatorium care. No positive gastrics or sputum. Lesion stable four years.
S. C.	M	1942	Neg.	Pos. Jan. 1942		Chest roentgenogram normal Jan., 1942. March, 1942, right apical disease with first interspace cavity. Gastrics positive. Sanatorium care for one year. May, 1947, questionable spread to right base. Sputum and gastric cultures negative. Cleared rapidly.

TABLE VII—Continued

Name	Sex	Class	Entr. Tbn.	Grad. Tbn.	Subseq. Tbn.	
N. B.	M	1943	Neg.	Neg.	Pos. Aug. 1945 (first tbn. test after grad.)	Diagnosis made in service July, 1945. However, review of previous roentgenograms showed "faint shadows in right first interspace" Sept., 1944, which had increased by July, 1945. Sanatorium care for four months with regressions. Gastrics negative. Lesion has been stable ("a 1 cm. fibrous nodule in right first interspace") since Dec., 1945.
R. G.	M	1943	Pos.	Pos.	—	First recognized 1 cm. lesion in left third interspace in April, 1943. Gastrics negative. No treatment. Lesion has remained fibrous in appearance and unchanged.
R. R.	M	1943	Neg.	Neg.	Pos. May 1944	May, 1944, chest roentgenogram normal. Nov., 1944, a 1 cm. lesion in right second interspace. Increased in size by Nov., 1945, after overseas duty. Sanatorium care Dec., 1945, to Sept., 1946. No positive gastrics. Lesion gradually clearing in Jan., 1947.
L. J.	F	1943	Neg.	Pos. Feb. 1943		In 1944 left apical lesion recognized but felt to be "old." Roentgenograms as student normal Feb., 1943. Instability of disease June, 1945. Gastrics positive then. Sanatorium care Nov., 1945, to present time. Still positive and lesion unstable. In June, 1947, left pneumothorax instituted.
W. L.	M	1943	Neg.	Pos. Dec. 1942		Pulmonary tuberculosis I. Right second interspace 1 cm. lesion noted Feb., 1947. Previous roentgenograms normal. Gastrics negative. Lesion slowly clearing Oct., 1947, after rest program.
N. K.	M	1943	Neg.	Pos. April 1943		Chest roentgenograms clear April, 1943, and Nov., 1943. Jan., 1944, infiltrate in left second interspace with possible small cavity. Sanatorium care for one year. No report on gastrics.
A. F.	M	1944	Neg.	Pos. Aug. 1944		Chest roentgenograms reported normal previously. Discharged from Army May, 1947, and moderately advanced pulmonary tuberculosis diagnosed. Receiving sanatorium care. Lesion in right first and second interspaces peripherally.
I. K.	M	1944	Neg.	Quest. pos. 1942		April, 1942, hilar adenopathy left and infiltration off left hilum. Gastrics negative. Sanatorium care April, 1942, to November, 1942, with little change. Returned to school with reduced schedule. September, 1943, small right pleural effusion. Tuberculin test then very strongly positive. Fluid cultures negative. Rest at home six months and effusion cleared. Lesion has been stable since, with possible slight clearing.

TABLE VII—*Continued*

Name	Sex	Class	Entr. Tbn.	Grad. Tbn.	Subseq. Tbn.	
R. S.	M	1945	Neg.	Pos. July 1942		1 to 2 cm. infiltrate in left mid lung in July, 1942, with very slight hilar lymphadenopathy. Lesion remained stable and still is, according to recent roentgenographic studies. No gastrics done.
C. F.	F	1945	Not known	Pos. when first tested as Jr. (transfer student)		No previous tuberculin tests done. Chest roentgenogram normal as student. During internship, minimal right apical tuberculosis diagnosed and sanatorium care. Still has active disease. Positive sputum cultures.
D. W.	F	1946	Neg.	Pos. Apr. 1944. Neg. incl. Feb. 1944		Chest roentgenograms negative April, 1944, to December, 1944. June, 1945, minimal infiltrate right third interspace peripherally. Gastric aspirations negative. Slight restriction in activity. Lesion stable to date with slight clearing in past six months.
R. J.	M	1946	Neg.	Neg. Apr. 1944 with 1.0 mg. O.T.	Pos. June 1946, 3+ to .01 mg. O.T.	Chest roentgenogram normal Feb, 1946. July, 1946, minimal bilateral apical disease. Gastric cultures positive. Bed rest sanatorium for one year with almost complete clearing of disease. Gastrics negative.
M. E.	F	1946	Pos.			Feb., 1946, chest roentgenogram clear. Hemoptysis Dec., 1946. Roentgenogram then showed bilateral subclavicular infiltrates. No positive gastrics but studies inadequate. Therapy at home with very little improvement.
S. R.	M	1946	Neg.	B.C.G.	Pos.	March, 1946, chest roentgenogram normal. Very minimal infiltrate noted Aug., 1946. Increased by Nov., 1946, left first interspace, then stable to date. Gastrics, six a.m. specimens, negative. Accepted by Navy July, 1947.
J. A.	M	1947	Neg. 1940	Pos. April 1945		Contact with tuberculosis as a ward helper Jan. to June, 1943. No tuberculin tests then. April, 1945, chest roentgenogram normal and remained so until Aug., 1946, when 1 cm. infiltrate in right first interspace noted. Six a.m. gastrics negative. Roentgen appearance has changed very little.

entire group of 188, this is 10.1 per cent; but if the 50 graduates who report they are still tuberculin negative are excluded, the incidence of tuberculous infection among the converters is 13.7 per cent.   In these same classes there are only two, or 2.1 per cent, of the original 95 tuberculin reactors who developed tuberculosis.   The tuberculin reaction of one entering student who developed tuberculosis is unknown, so he has been included in the tuberculin positive group.   In the second division of Medical School graduates, the classes of 1944 to 1947 inclusive, six of the 44 original tuberculin negative individuals have developed tuberculosis, or 13.6 per cent of the entire group. However, if the 10 who are still tuberculin negative are excluded, the incidence of tuberculous lesions among the converters rises to 17.6 per cent. Among 46 original tuberculin reactors (including one first tested as a third year transfer student), two have tuberculosis, or 4.3 per cent.   Of the 106 receiving B.C.G. vaccination, one individual has developed a minimal lesion during his internship.

The student nurses of the classes 1934 through 1944 show the same high incidence of tuberculous disease in the converting group.   Of the 112 graduates on whom we have adequate information, there were 89 tuberculin negative at entrance to nurses' training.   Of these, 30 report they are still tuberculin negative.   Eight of the 59 converters, or 13.6 per cent, have had tuberculous lesions.   Of the 33 originally tuberculin positive group, only one student has had tuberculosis, or 3 per cent.   This student entered training with bilateral apical infiltrates which showed very little roentgen evidence of change, although positive gastrics were obtained during her training course.   We believe her disease was active at the time she was admitted to training, although we have included her in the group developing tuberculosis. None of the student nurses has developed recognized tuberculosis in the classes graduating since 1944.   All except seven of the tuberculin negative student nurses in these classes have received B.C.G. vaccination.

An attempt has been made to determine the interval between tuberculin conversion and the first recognition of tuberculous disease.   As a large number of the medical students developed tuberculosis subsequent to graduation, tuberculin testing and chest roentgenograms were not repeated at regular intervals.   Therefore, an accurate statement as to the interval between infection and manifest disease cannot be made for the entire group.   However, in several the tuberculin conversion and the roentgen evidence were very closely correlated, as will be noted in the case summaries.   In one student who was out of school at the time of the recognition of tuberculosis, a far advanced caseopneumonic tuberculosis had developed within 15 months of a known negative tuberculin and six months after the recorded positive tuberculin.   With the exception of this student, the two with pleural effusions, and the one with hemoptysis, the recognition of tuberculosis was made by routine chest roentgenograms.   Several had reached a moderately advanced stage at the time of recognition, usually because of small cavitation in an acutely exudative lesion.

Among the student nurses, the interval between tuberculin conversion and roentgen evidence of tuberculous disease is better demonstrated. In three of the eight, the roentgenogram obtained at the time of the first positive test showed disease. In the others, tuberculosis was found within a period of three to nine months after the tuberculin conversion. As these students were tuberculin tested every six months, there was no interval longer than 15 months between the last recorded tuberculin negative reaction and the recognition of tuberculous disease.

The severity of the disease is noted in the case summaries. Among the tuberculin converters in the medical students there has been one death. Eighteen of the group received sanatorium care. In addition to bed rest, pneumothorax was instituted in four and thoracoplasty was considered necessary in one. Seven of the converters with small tuberculous lesions were allowed to continue their work with limitation of activity and are doing well to date. The course of the disease in the originally positive group is essentially the same, although there have been no deaths and no collapse therapy was used. The group is too small and the time under observation too short to permit any sound statement as to the relative severity of the disease. In the student nurses, the course of disease has been similar but no deaths have occurred. Only one student required thoracoplasty to control disease, and pneumothorax was used in one individual. The others cleared by rest alone. In three of the group, the students were limited in their activities and were able to control the disease process.

The failure of bacteriologic confirmation of our diagnosis in some of these students will raise questions as to the validity of our diagnosis. However, in minimal lesions the failure to demonstrate tubercle bacilli by repeated studies is no adequate reason to exclude the diagnosis in a tuberculin sensitive individual in whom the roentgen evidence exists. Before the widespread acceptance of gastric aspirations for the demonstration of tubercle bacilli in the patient unable to supply an adequate sputum specimen, a few of the moderately advanced lesions were not confirmed by actual demonstration of the organism.

The roentgen findings in the tuberculous individuals have been indicated in the brief case summary. The most common location of the parenchymal lesions is in the upper lung field, especially in the infraclavicular area. In three individuals, minimal hilar adenopathy was observed in addition to the parenchymal focus. From the roentgen appearance alone it is impossible to distinguish the disease occurring shortly after tuberculin conversion from the minimal "re-infection" type of disease which commonly occurs in this same location. In those with hilar adenopathy, the roentgen appearance is the same as that observed in children, although in none of the three observed did the adenopathy reach the degree frequently associated with primary tuberculosis in younger individuals.

Of particular interest is the group of medical students who had hilar adenopathy without recognized parenchymal disease. In one the diag-

nosis of "hyperplastic tuberculosis" was made from a cervical node biopsy. At the present time this would be classified as sarcoidosis.   In the remainder of the group biopsy proof is lacking, but this diagnosis must be considered in view of the benign course.

In student O. O. the tuberculin anergy during the course of the disease was followed by reactivity to tuberculin after the mediastinal adenopathy had regressed.   Although Hodgkin's disease can not be excluded, the course is unusual for that disease.   In student F. G., the mediastinal adenopathy following tuberculin conversion would lead to the diagnosis of primary tuberculosis without recognized parenchymal focus.

The occurrence of mediastinal adenopathy in this group is higher than that usually recorded for sarcoidosis; however, it is impossible to make an accurate comparison because of the high frequency of roentgen examination in this group.   The etiology of sarcoidosis is unknown, although several workers have favored a tuberculous infection of a noncaseating type.   If in the future a higher incidence of sarcoidosis can be demonstrated in a group exposed to tubercle bacilli, this position might be strengthened.

DISCUSSION

The reports in the literature disclose little uniformity of opinion as to the liability of tuberculous infection in the tuberculin negative student and in the tuberculin reactors.   In a recent report Brean and Kane [2] state that "although the nature of the tuberculin reaction of the medical students on entrance played no demonstrable rôle in the subsequent development of pulmonary tuberculosis, the conversion from the nonreactive to the reactive state while in medical school carried a liability greater than 5 per cent that the disease would develop before graduation."   They also state: "The incidence of significant active adult type tuberculosis in Harvard Medical School was 2.2 per cent."   These two statements are difficult to correlate. In 1941 Isreal et al. [3] reported that there was only slight difference in the tuberculin positive and tuberculin negative individual in the incidence and character of the tuberculous disease of the nurses studied.   Thirty-four of 277, or 12.3 per cent, developed tuberculosis in the original tuberculin negative, as compared to 34 of 360, or 9.4 per cent, in the original reactive group. Badger and Ritvo [4] likewise report that there was little difference in morbidity in the two groups.   Nine of 291, or 3.1 per cent, in the original tuberculin reactors developed tuberculosis, as compared to 12 of 219, or 5.5 per cent, in the original tuberculin negative group.

Daniels [5, 6] records a significant variation.   He reports a morbidity among student nurses to be two and one-half times lower in the original tuberculin reactor than in those who entered training in tuberculin negative. From his survey there were 43 cases of tuberculosis in 2,120 originally tuberculin positive nurses, or 2.0 per cent, as contrasted with 27 cases among 452 original nonreactors, or 6.0 per cent.   From a collection of 20 other

surveys, including 10 from the United States, they summarized the results as follows: 8,202 initial tuberculin reactors showed 173 cases of tuberculosis, or 2.1 per cent. Of 4,832 nonreactors at the beginning of training, 278, or 5.8 per cent, developed tuberculous disease.

Heimbeck's [7] figures are probably the most striking in a large series. Of the original tuberculin negative group, 13.8 per cent developed disease, as compared to 3.2 per cent among the original tuberculin reactors. A recent report of Meade's [8] at the University of Rochester Medical School gives a very comparable figure. Of 138 students who were reactors on entrance to training, four, or 2.89 per cent, developed tuberculosis before graduation. Of 175 students tuberculin negative on entrance, 27, or 15.4 per cent, developed tuberculosis.

Wright [9] reports the incidence of tuberculosis in two classes of student nurses at the Royal Victoria Hospital. From further breakdown of his table to make it comparable to Heimbeck's and Meade's reports, the following results are obtained: Among 144 students, there were 105 who were tuberculin negative on entrance and 30 still negative on completion of their training. In these 75 converters there were 10, or 13.3 per cent, who developed tuberculosis. Among the 36 originally tuberculin positive student nurses no tuberculosis was recognized.

The incidence of tuberculous disease in Heimbeck's, Meade's and Wright's reports shows a striking similarity to our experience. Our incidence of tuberculosis in the converting students was 13.7 per cent, 17.6 per cent and 13.6 per cent in the three divisions. Likewise, the original reactors were quite similar: 2.1 per cent, 4.3 per cent and 3.0 per cent developed tuberculosis.

In several articles, continued exposure of the recently infected individual is stressed as the factor chiefly responsible for the development of subsequent manifest tuberculosis.[10, 11] This does not appear to be a significant factor for several reasons.

First, although our rate of tuberculin conversion is low compared to many of the previous studies, we have experienced as high or higher incidence of tuberculosis. It seems improbable that the students, once infected (as evidenced by tuberculin conversion), could have had repeated contacts with the tubercle bacilli while many of their classmates escaped infection entirely. As noted in the student nurses, tuberculin conversion among the negative group varied from 14 per cent to 42 per cent during their training. In addition to this observation, the rapid development of the subsequent tuberculous disease is hard to correlate with the theory of continued exposure subsequent to that exposure which resulted in the tuberculous infection. In our study, the incidence of tuberculosis is not greater in the group which was under the longest period of observation, but is highest in the most recent group of medical school graduates. The most challenging opposition to the theory of repeated exposure is the benefit these individuals obtain from sanatorium care where continued contact is probable.

Tuberculosis remains one of the important occupational hazards of the student nurse and medical student.   Our approach to this problem must be a realistic one, for until such time as tuberculosis is eradicated this problem will continue.   These students deserve protection from tuberculosis both recognized and unrecognized.   The protection is simple where tuberculosis is recognized, as ordinary infectious disease precautions are highly efficient in the control of dissemination of the tubercle bacilli.   The unrecognized case of tuberculosis is a much greater problem.   In spite of screening methods now employed in many hospitals, tuberculosis is still overlooked in some cases.   Unless the students are not permitted contact with any patient until he is proved free from tuberculosis, the hazard of tuberculous infection exists, although admittedly it is much lower than where no attempt at screening is made.   With this attitude, however, the student is not prepared to recognize tuberculosis.   Adequate training in tuberculous disease is essential.   We must convince the student through his own experience that any patient may have active pulmonary tuberculosis.   Furthermore, any patient who is raising sputum or spitting blood must be considered as tuberculous until adequate search for tubercle bacilli has failed to demonstrate them, regardless of the physical findings, course of the disease, and the roentgenographic appearance of the chest.

In addition, the students must be trained that routine roentgen chest examination and tuberculin testing are as essential after graduation as when this responsibility is delegated to someone else.   The responses from the medical school graduate were somewhat discouraging.   One physician replied that he had never had tuberculosis and that all his chest roentgenograms were on file in our department.   The fact that he had been graduated seven years before did not seem adequate reason for another chest roentgenogram.

In addition to the control of the environment to prevent contact with the tubercle bacillus, some consideration must be given to the factor of immunity.   The lower incidence of tuberculosis in the original tuberculin reactor in many of the reported studies as well as animal experiments indicates that there is some protection from a previous controlled infection.   The tuberculin positive individual must be regarded as belonging to a selected group, as some of the infected group have already been eliminated by progressive tuberculosis.   The natural acquisition of tuberculin sensitivity is not without hazard, but from a purely practical viewpoint we cannot exclude tuberculin negative individuals from these professional courses.

The immunity conferred by B.C.G. is worthy of trial.   It is admitted by the severest critics of this method that B.C.G. vaccination is harmless.   The recent reports indicate that some degree of protection is afforded the tuberculin negative individual who is in an environment where tuberculous infection is excessive.   The opponents' chief objection seems to be that we will confuse the picture by eliminating the diagnostic significance of the tuberculin test.   However, when we considered the fact that approximately

14 per cent of the naturally acquired tuberculin conversion resulted in evidence of tuberculous disease, we were willing to sacrifice this diagnostic test. The same charge could be made against several other accepted forms of immunization.

Since 1942 we have vaccinated 245 medical students and 174 student nurses with B.C.G., using the multiple puncture technic as advocated by S. R. Rosenthal. There have been no systemic reactions, local abscesses, or regional adenitis. With two exceptions, all of the vaccinated individuals have become tuberculin sensitive. In these two individuals the local reaction was the same as usually seen, and we have no explanation for the failure to produce tuberculin sensitivity to 1.0 mg. O.T. The tuberculin reactions have remained positive throughout the period of professional training and, in the questionnaire response, the percentage of positive reactors remained high. At this time the length of observation does not justify any attempt to complete a report on the length of tuberculin sensitivity with B.C.G. vaccination and the many other factors which must be included. However, we do feel that our experience with B.C.G. is very encouraging. Only two vaccinated students have developed pulmonary lesions which might be considered tuberculosis. The one student mentioned previously has a minimal infiltration in the left apex but no tubercle bacilli have been recovered. In spite of continuing an active internship his lesion regressed. The student V. M., included in the group of mediastinal adenopathy, presumably has sarcoidosis.

From our own experience here we believe that B.C.G. is of value in the control of tuberculous disease, although the period of observation is short. We have not and do not intend to relax any recognized method of control of tuberculous infection. Our tuberculin conversion rate has never been high, but in spite of this our incidence of tuberculous disease among the converters is high. Therefore, we do not feel that the mere reduction in tuberculous infection is the ultimate goal, however worthwhile this objective may be.

CONCLUSIONS

1. Tuberculosis is a disease which requires the attention of all individuals who are concerned with the health problems of medical and nursing personnel. The problem is universal but with great individual variation, due to local differences of tuberculin sensitivity and opportunities for tuberculous infection.

2. Tuberculosis in our experience occurred more frequently in the original tuberculin negative individuals than in the original tuberculin positive individuals. Thirty-three, or 14.3 per cent, of the 231 tuberculin converters developed tuberculosis, as compared to five, or 2.9 per cent, of the 174 original tuberculin reactors.

3. Environmental control of tuberculous infection is worthy of continued close attention. However, until tuberculosis is eradicated, tuberculous in-

fection will occur in spite of the most rigid program. This is particularly true if the continued exposures and experiences of these professional groups be considered.

4. B.C.G. vaccination is worthy of trial in any group where the opportunity for tuberculous infection is high. At the present time this group includes all tuberculin negative individuals whose occupation brings them into close contact with the sick.

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AN OUTBREAK OF PRIMARY PULMONARY COC-
CIDIOIDOMYCOSIS IN LOS ANGELES
COUNTY, CALIFORNIA *

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Introduction

Concentration of troops in the southwestern United States during
World War II resulted in the knowledge that areas other than the San
Joaquin Valley are endemic for coccidioidomycosis.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,
14, 15, 16, 17, 24, 45, 47] Because the Los Angeles County Hospital receives pa-
tients from all parts of this large county, many of whom have worked in
adjoining areas, a number of cases of coccidioidomycosis are observed each
year. The present study was undertaken because of the simultaneous ad-
mission of three young men with a symptom-complex of a respiratory nature
which was subsequently determined to be primary pulmonary coccidioido-
mycosis. Further, these patients had all come from the same Forestry
Camp near Saugus, California. Here was afforded an excellent opportunity
to study a group of young males whose period of confinement to a specific
geographic area was definite, whose work was similar, and whose activities
were well documented. Most important, these are the first cases definitely
known to have acquired their infection in Los Angeles County, although
from a review of the histories of cases seen in this hospital the endemicity
of the area had been suspected.[18]

An extensive literature on primary coccidioidomycosis has appeared in
recent years but no comprehensive summary has been made. In an attempt
to evaluate and correlate the data pertinent to this study the following review
is presented.

The most accurate procedures for the diagnosis of coccidioidomycosis are
the demonstration of *Coccidioides immitis* by direct mount, culture, and ani-
mal inoculation. In the primary pulmonary phase this demonstration may
be extremely difficult, for to date the best result reported is 61 per cent.[6]
Because of the infectivity of the arthrospores from cultures, these procedures
are dangerous and are therefore best performed by experienced personnel.
Further, the differentiation of the tissue stage from other fungi requires the
presence of endospores within spherules for final diagnosis.[20] Because of

these difficulties, skin tests and serologic tests are used more extensively for practical diagnostic purposes.

The earliest reports of positive coccidioidin reactions were made by Jacobson.[48] Later investigators questioned the specificity of coccidioidin reactions.[49] However, Kessel[23] and Aronson[24] found that cross reaction with tuberculin did not occur. Later Smith[22] and others also demonstrated its specificity and recommended its use as an aid in diagnostic and survey procedures. More recently Emmons, et al.[25] show that cross reactions may occur between certain heterologous fungus antigens, e.g., histoplasmin and blastomycin, and to a lesser extent between these and coccidioidin. Smith, et al.[26, 50] agree with Emmons that cross reactions may occur with histoplasmin, but more commonly in low dilutions of the coccidioidin antigen. They state that coccidioidin did not cross-react to a degree which interfered with interpretation.

Positive skin tests usually appear two to three weeks after clinical onset,[21] and it is generally accepted that a change from a negative to a positive skin test reaction in a patient under constant observation in a restricted geographic area is acceptable evidence of infection. It is now considered that 1:100 is the dilution of choice for routine diagnostic and survey purposes, because it gives the maximum number of positive reactions with a minimum number of non-specific responses. The correlation of the change in intensity of the skin test reaction with the probability for dissemination or recovery has been discussed by Smith, et al.[21] They state that a strong reaction is a good indication for recovery, except in cases of meningitis, while the lessening of the skin test in the face of continued symptoms is an ominous prognostic sign.

In the past it has been assumed that skin sensitivity, once acquired, lasts for life. It must be remembered that the early work was done in the San Joaquin Valley, a highly endemic area where opportunities for reinfection or resensitization are maximal. Smith[21] presents evidence that sensitivity is retained for at least a year, and quotes records of positive skin tests in asymptomatic individuals after years of residence outside of an endemic area. However, Cheney and Denenholz[9] recently reported the loss of skin sensitivity six to eight months after first appearance of a positive reaction, all positive reactors in their series becoming negative within a year.

Early universal failures in agglutination, precipitin and complement fixation tests were reported by several investigators.[43, 44, 45] The first successful precipitin and complement fixation tests for coccidioidomycosis were accomplished by Smith.[22] The precipitin test is a four tube test beginning with undiluted patient's serum and continuing by half dilutions through the four tubes. The complement fixation test is similar to the quantitative Kolmer test for syphilis.[22] In relation to the clinical course of the disease, Smith found that the precipitin titer rises early in the primary pulmonary infection and falls at about the same time that the complement fixing antibodies begin to rise. The two tests may subsequently run parallel for a brief period. While the precipitin antibodies rise early and fall quickly, the complement

fixing antibodies may continue to rise to their peak, then diminish. The length of time that these complement fixation titers remain positive varies. Smith [22] states that in mild infections the serologic tests may never become positive, but the skin test will change over from negative to positive. The complement fixation and precipitin tests have been useful as an index of active disease and as a means of determining the probability of dissemination.[7, 10, 12, 17, 27] Willett and Weiss [6] report a definite correlation between the clinical course and results of complement fixation and precipitin tests. They further found the complement fixation test to be a useful index for ambulation of the patient. However, a few active clinical cases with negative complement fixation and precipitin tests have been described.[6, 10]

Eosinophilia, increased sedimentation rate, and polymorphonuclear leukocytosis are the more constant findings mentioned in the literature as occurring in coccidioidomycosis. The eosinophilia seems to be a rather persistent occurrence in many of the cases during the course of the disease. The percentage of patients showing an increased eosinophile count in recent epidemics ranged from eight to twenty-three.[7, 10, 17] Willett and Weiss [6] gave no exact figure but indicated that most cases showed an eosinophilia at some time during the primary pulmonary infection. A single case with an eosinophil count as high as 87 per cent is recorded.[22]

An increase in the sedimentation rate appears as a frequent accompaniment of active disease in the reported cases. Return to normal was used as a criterion for permitting the patient to resume activity.[6, 22] In recent primary epidemics 75 to 100 per cent of cases reported had elevated sedimentation rates.[6, 7, 10, 17]

Leukocytosis varied in incidence from 35 per cent to 70 per cent.[6] In most cases this was during the early stage of the pulmonary infection. Nowhere is any mention made that atypical white cells were encountered. This is of interest in relation to the results in the cases here reported.

In the primary pulmonary phase of coccidioidomycosis, symptoms are varied, protean in nature and in no way diagnostic of the disease.[6, 7, 27] The symptoms are essentially those of an upper respiratory infection, in which fever, non-productive cough, and chest pain, particularly substernal in nature, were most frequently encountered. There may also be malaise, chills, pleurisy, and headache. While the above symptoms are more common, they are also seen in a wide variety of other syndromes. Among the less frequent findings pointed out as helpful in the diagnosis of the disease are joint pains, conjunctivitis, cervical adenopathy, erythema multiforme, and erythema nodosum. Early papers published on primary pulmonary infection placed great stress on the appearance of erythema nodosum as an outstanding sign.[1, 2, 3, 4] In subsequent outbreaks the rates of occurrence of erythema nodosum are lower, varying from 4.4 per cent to 20 per cent.[6, 7, 10, 17] There are few physical findings to distinguish the primary phase of this ailment from other syndromes, such as atypical pneumonia, infectious mononucleosis, brucellosis, tuberculosis, influenzal syndrome, etc. When erythema nodosum

or erythema multiforme accompanies any of the above symptoms, together with a pertinent history of recent residence in a known endemic area, one should direct his attention to coccidioidomycosis. In the absence of erythema nodosum or erythema multiforme, the logical diagnostic alternatives are therefore general and specific laboratory procedures. However, it must be remembered that there are some who pass through the primary phase of this disease without any clinical manifestations whatsoever, and whose only evidence of past infection is a positive skin test or residual roentgenographic findings.[19, 28]

Roentgenographic changes in the chest and other bodily organs in coccidioidomycosis are varied and are relatively non-specific.[10, 28, 29, 30, 31, 32, 33] However, certain patterns or processes are characteristic of this disease. For practical purposes, serial roentgenograms may be difficult to obtain but, as has been aptly stated by Carter, "serial roentgenograms probably provide the key to the roentgenographic diagnosis."[33] The earliest lesion is characteristically that of an infiltration which may vary from slight fuzzy thickening of the hilar shadows to extensive consolidations occupying a major portion of the lung field. The infiltrations vary in density from a light veil-like haze to the opacity of lobar pneumonia. Difficulty may be encountered in differentiating these from atypical pneumonia or rheumatic pneumonitis.[34]

The aforementioned lesions may clear, leaving no residua, or only a few strands, or they may progress to a protracted form of primary coccidioidomycosis in which multiple cavities are evident in a zone of confluent infiltration.[28] When multiple cavities are present in the upper lobe, the roentgenologist almost always labels these tuberculosis of the advanced ulcerative type. Here the importance of serial roentgenograms is demonstrated, since the majority of these lesions clear with a rapidity never seen in tuberculosis. Mediastinal adenopathy accompanies many of the severe or protracted coccidioidal infections. The rapid appearance of mediastinal lumpiness or nodes, combined with the early infiltrative lesion, is one of the most characteristic radiologic findings of this disease. Some authors do not place so much stress upon the adenopathy.[35]

Pleural effusion is mentioned as being one of the uncommon manifestations of the primary pulmonary disease and, when present, it is usually of minimal amount.[32] However, one of the cases in this study developed a massive pleural effusion within five days after entering the hospital. Many of these early manifestations are missed, either because they appear and disappear with such astonishing rapidity or because the initial symptoms are so vague and ill-defined that the patient does not consult a physician. Then the so-called "indolent lesions" of burned-out coccidioidomycosis become important in diagnosis.[28, 29, 36] These have been described as irregular nodular lesions scattered in both lungs without any characteristic distribution, thin-walled cavities represented by ring-like shadows, so well described by Winn[28] and found so often in reports of series studied by the Army in World War

II. It must be emphasized that a patient in an acute febrile phase may also exhibit the above lesions.

Finally, there are the calcifications, large and small, discrete and scattered, often associated in the past with healed coccidioidomycosis and more recently also with histoplasmosis.[37] These nodularities and cavities appear to be quiescent, since a surrounding zone of infiltration is practically never seen. Prognosis is generally good, although it may be years before the cavities are obliterated. Usually no treatment is necessary and pneumothorax is resorted to only in cases of hemorrhage, etc. As will be seen, the cases in this study exhibited most of the above primary findings in one form or another, with adenopathy being a prominent finding.

It is unfortunate that knowledge of therapy in coccidioidomycosis has not kept pace with information concerning the clinical and immunologic aspects. It was Jacobson[39, 40] who first reported any extensive use of specific therapy in disseminated coccidioidomycosis. He originally recommended the use of colloidal copper, but subsequently developed a specific antigen which he has used extensively and with which he has reported favorable results. Unfortunately, there have been no further reports on its use in recent years. Lately, in reports of cases collected by the Army, sulfonamides, penicillin and immune serum, from patients with recent disease and high precipitin titers, have all been uniformly disappointing in therapy except in isolated instances. In a recent case in this hospital aureomycin was given without appreciable benefit to the patient. Rest, nutritious diet, symptomatic care, and knowledge of when it is advisable to permit the patient to return to activity seem to be all the therapy that is available at the present time.

Since the clinical course of the disease has been well described, it is recognized that the transient primary pulmonary phase carries no mortality per se. It is only in the secondary or disseminated form that mortality is high. In disseminated cases the mortality rate is approximately 50 per cent.[22] There is a great deal of evidence to point to racial differences in rates of dissemination. From statistics previously available, it is shown that in white males the number of clinically diagnosed primary cases which disseminate is considerably less than one half of 1 per cent, while in the dark skinned races the dissemination rate is at least 10 times as great.[19] However, Willett and Weiss recently report a combined Negro and white dissemination rate of 4 per cent and in Negroes alone the rate was 12 per cent, which is high in comparison with previously reported figures. In the white race, three out of every eight cases that disseminate die of the disease, while the figure is higher in Negroes. In white males, dissemination occurs more frequently to the meninges, while in the dark males dissemination is most often generalized, i.e., bone, skin, etc. Since the mortality rate is approximately 50 per cent in disseminated cases, it becomes important to detect dissemination early and, if possible, to prevent it.

The greatest divergence of opinion exists concerning the length of time from the primary attack until dissemination may take place. Smith[19] and

Butt [41] both believe that dissemination, when it occurs, does so at an early date, probably within a year after onset of the primary pulmonary disease. Forbus and Bestebreurtje [42] in a recent study at the Army Institute of Pathology, state that clinically healed coccidioidomycosis may serve as a source of disseminated infection months or years after pulmonary disease has disappeared. Thus the problem as to when the patient is sufficiently well to become ambulatory, and when the danger of dissemination has disappeared, is of great importance to both the physician and patient. Therefore, it is essential to consider a reasonable criterion for ambulation of the patient. The return of the sedimentation rate to normal, coincidental with the absence of clinical signs, has been used as this criterion by most investigators. Only in Willet and Weiss' [6] recent series is a falling titer or absence of complement fixing antibodies also used as a basis for ambulation of the patient. Forbus and Bestebreurtje [42] state that the average duration of the disease in 50 fatal cases of coccidioidomycosis is 104 days, the shortest being 25 days and the longest 467 days from onset.

CURRENT STUDIES

The first three patients observed in this study were admitted to Los Angeles County Hospital on September 29, 1948, with a febrile illness of a respiratory nature. This was subsequently determined to be primary pulmonary coccidioidomycosis. They were part of a group of 61 boys in a camp in which several others had been ill with similar symptoms at the same time. It was considered that further study of the entire group was indicated.

Epidemiologic Studies. The first trip to this camp was made on November 1, 1948, to obtain clinical and careful epidemiologic histories, give skin tests, and procure blood for precipitin and complement fixation tests from the entire group. Those boys showing a positive reaction to skin or serologic tests were given a limited physical examination and chest roentgenograms were taken. Whenever possible, these chest films were compared with previous films. Two subsequent trips approximately one month apart, were made to the camp to repeat the skin tests and draw blood for complement fixation tests.

During the course of this study it was fortunate that a group of 45 boys were transferred from another camp. This second group, because they were new arrivals in the area and were of the same age, sex, and occupation, served as controls. They were given skin tests and blood was taken for complement fixation tests within one week after arrival.

The coccidioidin used for skin test antigen was prepared in the Los Angeles County Hospital, using Long's synthetic medium as recommended by Smith.[22] The coccidioidin was prepared from *C. immitis* recovered from seven different clinical cases from various geographic regions. This antigen (A_1) has been used in this hospital and surrounding area for some years and has proved to be both sensitive and specific. Two dilutions were used, 1:100 and 1:10.

The histoplasmin used in this series is Lot H-3 from Dr. C. W. Emmons and was furnished through the courtesy of Dr. C. Palmer.   It was used in a dilution of 1:1000.   Some of this group of boys also had tuberculin tests (PPD No. 2).   All skin tests were performed and read by the same person 48 hours after injection.   Only those reactions which had more than 5 mm. of induration with or without erythema were recorded as positive.   Erythema alone was not of diagnostic value.

The coccidioidin antigens used for complement fixation and precipitin tests were identical with the skin test antigen, and have been used in the Los Angeles County Hospital laboratory for hundreds of cases with satisfactory results.   There is no evidence to date that cross reactions occur with sera from cases of blastomycosis, cryptococcosis, actinomycosis, or syphilis. In the entire survey, a two tube screening test was used, and the positive sera were then titered in the routine eight tube complement fixation test.   None of the sera was anticomplementary.   A three or four plus fixation in the first tube was considered positive and interpreted as an index of infection.   In the course of this study, a number of equivocal or plus-minus reactions were encountered.   These were given no significance per se, but sera from these boys were subsequently collected and retested to determine whether the reaction had become positive or negative.

TABLE I

Skin Test Reactions from Survey Group

	Total No.	Coccidioidin Skin Test		Histoplasmin Skin Test	
		Pos.	Neg.	Pos.	Neg.
Study group	61	20	41	4	52
Control group	45	5	40	4	41

By the use of serial skin tests, complement fixation tests and roentgen-rays, correlated with physical findings, four additional active cases were detected and hospitalized.   This resulted in a total of seven hospitalized cases from the entire group.

Including the hospitalized cases, the results of the skin test studies are shown in table 1.

Of the total number of skin tests, it is seen that 20 of 61, or 33 per cent. were positive.   In the control group 5 of 45, or 11 per cent were positive. A correction was necessary for those who had lived in an endemic area, i.e., the San Joaquin Valley, Texas, Arizona, etc.   Since the duration of skin sensitivity has been reported recently to last at least one year, three years was selected in order to provide a margin of safety.

When this correction for residence was made, it was found that 16 of 57, or 29 per cent, were positive in the study group, while in the control group only 7 per cent were positive.   This difference is statistically significant.

TABLE II
Skin Test Reactions Adjusted for Residence Data

	Previous Residence in Endemic Area	Corrected Total from Table 1	Positive Cases without Residence in Endemic Area
Study group	4	57	16
Control group	2	43	3

It is reasonably well established that a change-over in skin test reaction within a short period of time from a negative to a positive reaction is indicative of recent infection. It is therefore pertinent to point out that of the 20 positive skin test reactors, 7, or 35 per cent, showed a conversion from negative to positive during the course of the study. The wide difference between positive reactors in control and study groups, as well as the high percentage of recent converters, presented adequate evidence of the endemicity of this area in Los Angeles County for coccidioidomycosis.

Both study and control groups were given coccidioidin and histoplasmin skin tests simultaneously, and approximately 8 per cent of both groups had positive histoplasmin reactions. This was independent of the number of positive coccidioidin reactions. In the study group, all boys who showed a positive histoplasmin test also had a positive coccidioidin test. However, residence history showed that 75 per cent of the histoplasmin positive reactors had lived previously in an area known to be endemic for histoplasmosis. Further, among the 20 positive coccidioidin skin tests in the study group, only those four with a suspicious residential history showed positive histoplasmin tests. While the above numbers are too small to be of statistical value, they demonstrate that cross sensitivity of these two heterologous fungi as used in this study was minimal.

With the endemicity of the area established by skin tests, it was desirable to determine whether the positive tests were signs of current infection or of past sensitization. Table 3 therefore compares the complement fixation tests of both groups of boys. It is seen that in the study group 10 of 61, or 17 per cent, gave positive complement fixation tests, while there were no positive serologic reactions observed in the entire control group. This further substantiated the fact that this was an outbreak of active coccidioidomycosis. As already indicated, seven of the 10 boys exhibited symptoms sufficiently serious to warrant hospitalization.

TABLE III
Complement Fixation Test for Coccidioidomycosis

	Total No.	Pos.	Neg.
Study group	61	10	51
Control group	45	0	45

In the initial complement fixation tests on the study group, 12 tests gave an equivocal reaction. Serial testing revealed that seven of these subsequently became negative, while five developed positive reactions. Clinical findings gave corroboration of active infection in these five. If these equivocal reactions had been regarded as negative, or dismissed without further testing, a few boys with active infection might have been missed. Therefore, it is concluded that an equivocal test is an indication for subsequent serologic checking.

A study of the records showed that the original hospitalized cases were all members of one road crew that had worked in a nearby canyon during the month preceding the onset of illness. In an attempt to delineate more accurately the area of origin of the infection, the entire study group was divided into "road crew" and "non-road crew" members. Of the 61 in the original group, 33 were road crew members, and 50 per cent of these showed positive skin test reactions to coccidioidin. Of the 28 non-road crew members, only 18 per cent exhibited positive skin test reactions. A significant finding from this division was that all cases subsequently hospitalized were also members of this road crew. While the relatively higher attack rate in the road crew may indicate an area of high infectivity, it does not designate this single

TABLE IV

Symptoms and Findings

	No. Cases	
Total	7	
Symptoms		
C.N.S.		
Headache	7	
Others	3	
severe		2
mild		1
Respiratory		
Cough	6	
productive	3	
Chest pain	5	
substernal		3
pleuritic		2
Sore throat	4	
Epistaxis	2	
Anorexia and malaise	4	
Weight loss	2	
Nausea and vomiting	1	
Physical Findings		
Fever (range 100°–105°)	7	
Pharyngitis	7	
Lymphadenopathy (generalized)	4	
Pulmonary findings	1	
C.N.S. findings	1	
X-Ray Findings (Chest)		
Adenopathy	3	
Fibrosis	3	
Infiltration	2	
Effusion	1	
Consolidation	1	
Cavities	0	

TABLE V

Laboratory Findings

	Range	Average
White Blood Cells		
Total number	6,000–14,200	8,300
PMN	40%–81%	65%
Lymphocytes	22%–40%	30%
Eosinophiles	3%–11%	5 cases had eosinophilia
Sedimentation Rate (Wintrobe, corrected)		
Normal	3 cases	
Increased	4 cases (range was 10 mm.–48 mm./hr.)	
Sputa and Gastric Washings		
Total number done	20 (average was 3 per case)	
Positive on direct mount	1	
Positive on culture	0	
Spinal Fluid		
Total number of cases examined	3	
Positive on direct mount	1	
Positive on culture	1	

	Cases Examined	Result
Coccidioidin Tests		
Complement fixation (blood)	7	
Positive		6
Negative		1
Complement fixation (spinal)	2	
Positive		1
Skin test	7	
Positive		7

area as the sole source of infection, since 18 per cent of the non-road crew members also gave positive reactions, in contrast to 7 per cent in the control group. However, *Coccidioides immitis* was not recovered from samples of dung or soil from this area using the method described by Stewart and Meyer.[46]

The symptoms exhibited by the clinical cases are given in table 4. The most outstanding symptom was headache. All patients complained of this at the onset of illness, and the location varied from frontal to retro-orbital and occipital. Cough was quite common, although it was described as productive only in about half of the cases. A history of chest pain was particularly impressive and was present in 80 per cent of the cases. This was substernal in location in some, and generalized and pleuritic in nature in others. Sore throat, anorexia, and malaise, while fairly common, were not outstanding symptoms. As can be seen, the symptoms were those commonly associated with any febrile illness, with respiratory complaints predominating.

It is of interest that all patients ran an elevated temperature for some period of time during their illness. For the most part, by the time they were hospitalized, the temperature was only minimally elevated, the exception being 105° F. in one case (Case 1) coincidental with a massive pleural effusion. It is noteworthy that the patient gravely ill with meningitis (Case 7) never developed a temperature higher than 101° during his entire stay in the hospital, which correlated with his paucity of symptoms and physical findings. It is remarkable that few physical findings were present in the entire group.

A mild pharyngitis was seen in all patients on and shortly after admission. Two patients developed epistaxis and one a mild conjunctivitis. Pulmonary findings were noticeably lacking except in the case with massive pleural effusion. A common finding in our series was generalized lymphadenopathy, which was seen in two-thirds of the cases. This assumes greater importance when correlated with the high percentage of abnormal lymphocytes found in the blood of these patients (see later). Only in the one case with meningitis were central nervous system findings present. These findings were not evident until one month prior to death, when signs of obstruction to the cerebrospinal fluid dynamics became apparent along with compression of the cord. Early in this case clinical findings were absent, even though the spinal fluid showed many lymphocytes and an increased protein. Two other patients who complained of stiff neck had entirely negative spinal fluids.

A summary of complement fixation, precipitating and skin tests for coccidioidomycosis on the hospitalized cases are shown in charts 1 and 2. These have already been discussed in a general way, but their correlation with the clinical course may be of value. All hospitalized cases showed a positive complement fixation titer with one exception (Case 2). This boy was quite as ill as the other patients admitted at the same time. Although he had a
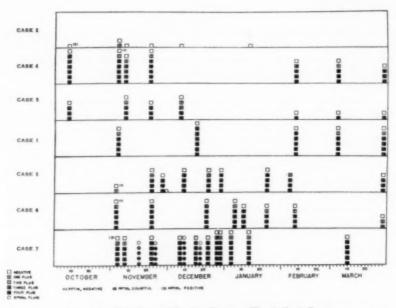
CHART 1. Complement Fixation Tests on Hospitalized Cases
The titer is read along the vertical line in each individual case using a routine eight tube test beginning with 0.2 c.c. of patient's serum and continuing in half dilutions.

positive skin test and definite radiographic findings (i.e., mediastinal lymph-adenopathy), he never developed a significant complement fixation titer. The complement fixation titer for each case rose early and remained at maximum limits for a considerable time after clinical symptoms disappeared. After some time this titer decreased to some degree in all boys who eventually recovered, although there was little correlation between the rate of decrease and complete recovery. The case which disseminated (Case 7) had consistently the highest complement fixation titer in the blood. However, another case (Case 1) who recovered from a massive pleural effusion had a transient titer which equaled the disseminated case. In the case of meningitis, the complement fixation titer of the spinal fluid on one occasion equaled the serum titer; otherwise the titer of spinal fluid was slightly lower than that of the sera. Six months after the onset of the disease, three of the six boys who are clinically well still exhibit an elevated though decreasing complement fixation titer.

	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH
CASE 2	3 CM.					
CASE 4 HISTO-NEG.	DOUBTFUL	0.7 CM.*				NEG. 0.7 CM.*
CASE 5 HISTO-NEG.	2 CM.					7 CM.
CASE 1 HISTO-NEG.	NEG.	6 CM.*				0.5 CM. 5 CM.*
CASE 3 HISTO-0.9 CM.		4.5 CM.				6 CM.
CASE 6 HISTO-NEG+		9 CM.	7 CM.			4.5 CM.
CASE 7	POSITIVE		7 CM.			1 CM.

CHART 2. Skin Test Reactions of the Hospitalized Cases
1/100 dilution of coccidioidin used and read in centimeters of induration, with or without erythema. * indicates reactions using 1/10 dilution of coccidioidin.

Five of the seven hospitalized cases, when first tested, had a positive coccidioidin skin test at 1:100 dilution, while two were negative. These two subsequently exhibited a positive test at 1:10 dilution, though still negative to the 1:100 dilution. The disseminated case gave a positive skin test in the 1:100 dilution as late as the last few weeks of life, but the skin test reaction had noticeably decreased in size.

The most suggestive of the non-specific laboratory tests was eosinophilia, which was present in five of seven cases at some time during the disease, with a range of 3 per cent to 11 per cent. It was our impression that the eosinophile count decreased in these cases coincidental with the subsidence of symptoms. The sedimentation rate repeated at intervals was elevated in four of seven cases. This did not seem to parallel the severity of symptoms, since some patients showed a transient elevation after all symptoms had disap-

peared.   Further, the boy with meningitis never had a sedimentation rate which exceeded 7.5 mm. in an hour.   Total white counts varied from a low of 6,250 to a high of 14,500, yet 90 per cent of the cases never exhibited a total count of over 10,000 during the course of their illness.   A finding which contributed to delay in establishing the diagnosis was the discovery of cells similar to Downey Type I lymphocytes in the smears of three patients.   The hematology department reported these as diagnostic of infectious mononucleosis.   Repeated heterophile agglutination titers on these patients, however, were negative.

In spite of repeated gastric washings and sputum examinations, *C. immitis* was demonstrated in only two cases on direct mount, and in one on culture confirmed by guinea pig inoculation.   It is surprising that clearly demonstrable organisms from gastric washings on direct mount are difficult to grow on culture, although this coincides with the past experience of this and other laboratories.[10]

Radiologic findings were demonstrable in six of our seven hospitalized cases.   Serial roentgenograms were taken on all of the hospitalized cases in this study.   These afforded an excellent series for review.   The chest roentgenograms collectively demonstrated most of the lesions usually attributed to coccidioidomycosis.   Mediastinal lymphadenopathy and pulmonary fibrosis were most prominent and occurred in three of the seven cases.   Infiltration and consolidation were also present (see table 4).   It is of interest that one case with massive pleural effusion (Case 1) cleared almost completely in a matter of weeks, leaving negligible residues.   Of the non-hospitalized cases, two demonstrated the thin walled ring cavities so well described by Winn.[28, 29]   This is illustrated in Case 8.   In Case 7 with coccidioidal meningitis, the only evidence of chest involvement was enlarged right paratracheal nodes.   This boy died and, on autopsy, *Coccidioides immitis* organisms were recovered from the enlarged node seen on roentgenogram.   In addition, there was a small focus in the peripheral pulmonary tissue which was not seen radiographically pre-mortem, from which *C. immitis* organisms were likewise grown.

DISCUSSION AND CONCLUSIONS

The admission of several cases of primary pulmonary coccidioidomycosis to the Los Angeles County Hospital, and a survey of the forestry camp near Saugus from which they came, demonstrated the first endemic focus of this disease in Los Angeles County.   These cases provided excellent material for a detailed clinical and epidemiologic study.

The value of repeated skin tests and serial complement fixation tests was established in the course of this survey on 61 boys of similar ages, having restricted and well catalogued activities.   The control group served as a base line of coccidioidin sensitivity from this county, and was especially valuable because there had been no previous reports of group skin testing with coccidioidin in this area.   A positive complement fixation test is, in the

opinion of the authors, very reliable evidence of either past or current active infection.

The importance of repeated complement fixation tests in routine surveys was established by the initial equivocal reactions, which subsequently changed to either positive or negative. Frequently the change from an equivocal to a positive reaction was accompanied by clinical signs of active infection.

The value of repeated skin tests with different dilutions was also evident, for in this survey an appreciable number of cases negative in the 1:100 dilution were subsequently positive in the 1:10 dilution and, when tested in this lower dilution, showed no more severe reactions. For surveys, therefore, the 1:10 dilution may be especially useful after preliminary screening with 1:100, since in this series there was a greater than the reported 10 per cent increase in the number of positives when this dilution was used.

Histoplasmosis as a clinical entity has assumed greater importance in recent medical literature. Further, epidemiologic studies concerning cross sensitivity with heterologous fungus antigens have indicated the importance of simultaneous coccidioidin and histoplasmin skin tests.[50] The members of both study and control groups were given histoplasmin and coccidioidin antigens, and approximately the same percentage of histoplasmin reactors was observed in both groups, regardless of the number of postive coccidioidin responses. The small total number of tests done, as well as the few positive histoplasmin reactors in this study, precludes any generalization concerning cross sensitivity. However, in this survey the majority of histoplasmin reactors showed resident histories compatible with specific sensitization. The presence of many coccidioidin positive reactors negative to histoplasmin makes valid the assumption that positive coccidioidin responses were not due to previous sensitization with histoplasmin. If cross sensitization between the antigens did occur, we feel that it was not sufficient to invalidate the conclusions of the current study. A more extensive series, using well-tested antigens, taking careful geographic histories and using standardized, measured readings, should provide evidence of cross sensitivity, if it exists.

Unfortunately, we were unable to recover *Coccidioides immitis* from samples of dung and soil in this area. This was not surprising in the light of past reports. The area in which these boys worked is dry and dusty for the greater part of the year, which confirms the impression that this type of climate and terrain is suitable for spread of the organism.

A great deal of the discussion of the hospitalized cases has been covered in the previous section, but a few pertinent problems deserve amplification. While the importance of residence in an endemic area has been emphasized in the literature and corroborated in this study, it must be realized that the areas of endemicity have not been completely worked out. Contiguous geographic areas with similar terrain and climate must be suspect. Had this been realized, the interval of time before diagnosis of the original cases would have been shorter. Since the symptomatology, as stated before, is non-specific, reliance was placed upon serial roentgenograms, serial comple-

ment fixation tests, and repeated skin tests. In the course of this study the following methods of investigation in suspected cases was found most valuable: In the presence of a pertinent geographic history accompanied by an upper respiratory infection, the first useful diagnostic procedure was the skin test in the 1 : 100 dilution. If this was negative, the 1 : 10 dilution was used. In the majority of primary pulmonary coccidioidomycosis cases one of these two dilutions will be positive. However, in patients with allergic manifestations (erythema nodosum), the 1 : 1,000 dilution should be used. In order to establish a base line of activity, if present, a complement fixation test is run. At the same time as complement fixation, or following a positive complement fixation test, sputa and gastric washings are cultured for the organism. It is necessary to secure several specimens from the patient, and these should be examined immediately after collection.[10]

Concomitant with these specific procedures, blood counts, sedimentation rates, and chest roentgen-rays should be completed. An eosinophilia is corroborative evidence of the disease. Although elevation of the sedimentation rate has been emphasized as one of the significant findings in this disease, in these cases it was not uniformly elevated. The diversity of findings in chest roentgen-rays has been discussed previously, and the rapid changes that can be seen in serial chest films were clearly demonstrated in these clinical cases. With one exception, all of the hospitalized cases had significant roentgen-ray findings, and we believe that the most frequently missed finding is a transient mediastinal lymphadenopathy. We were very fortunate in this regard to have Dr. Ray A. Carter read and interpret all the roentgenograms. His knowledge of radiographic findings in this disease was of inestimable value.

In following the course of these patients, greatest reliance was placed on subsidence or recrudescence of symptoms, serial roentgenograms, and serial complement fixations. The latter two were the most useful. There was no consistent change in degree of skin sensitivity in the hospitalized cases. In patients with primary pulmonary coccidioidomycosis, a rising complement fixation titer signifies an impending increase in severity of the disease. However, a drop in the titer did not necessarily accompany clinical improvement. There are patients who, six months after the disease, and completely asymptomatic, still show appreciable titer (see chart). In the absence of symptoms, a low or falling titer on monthly complement fixations should serve to reassure both the physician and patient of ultimate recovery. The high titer of the one meningitis case was matched, in a transient way, by a case of primary pulmonary coccidioidomycosis with pleural effusion. This latter case, however, has recovered and remains asymptomatic to date, with a concomitant decrease in complement fixation titer. In the case of dissemination to the meninges, the complement fixation of the spinal fluid revealed a titer only slightly lower than that of the blood, and it remained at this level until death. So far as we know, this is the first report of a spinal fluid complement fixation test performed simultaneously with that of the serum.

The time for ambulation of the convalescent patient with this disease is still unsettled.   Many of the Army reports convey the impression that these patients were kept at absolute bed rest for months at a time.   It was decided to permit gradual ambulation in patients who were symptom-free, whose roentgenograms were static or showed signs of regression of lesions, and, most important of all, whose complement fixation titer was not increasing or, preferably, was decreasing.   Patients were followed at bimonthly periods and discharged from further observation when the complement fixation titer had fallen to very low levels or was non-existent.   In retrospect, with regard to these seven hospitalized cases, a word may be said about necessity for hospitalization.   In the case with coccidioidal meningitis, the patient was completely asymptomatic during the first two months of his disease, even though he showed increased cells and protein in the spinal fluid.   It was only after a resultant arachnoiditis caused a block of his cerebrospinal fluid circulation that he became bed ridden and died a short time later.   Patients in this study were hospitalized because they could not be cared for at work camp.   In a social level where intelligent cooperation may be expected, hospitalization may not be necessary.   The primary disease is for the most part self limiting.   The symptoms, while severe at first, usually respond to non-specific symptomatic care in a short time.   Roentgenograms, serial complement fixation tests and sedimentation rates are preferably done at monthly intervals.   In addition, man-to-man transmission of this disease has never been reported to date.[36]   We believe that bed rest at home can be carried out successfully and with less expense to the patient.

<center>CASE REPORTS</center>

Case 1.   A 17 year old white male entered the hospital on September 27, 1948. The patient was born in Arizona, lived in and around Los Angeles, and recently had been working in a juvenile delinquency camp near Saugus, California.   A note from his outside physician stated that the patient had shown "a temperature of 102° F. and above for two days and chest pain for some length of time; upper respiratory infection with probable lung involvement."

A careful history obtained on entry revealed that the patient's symptoms started six days prior to entry.   At that time, he developed pain in the left side of his chest, aggravated by movement, deep inspiration, and laughter, accompanied by headache, weakness, malaise, anorexia, and a fluctuating temperature which had been as high as 102° F.   There was no history of cough, dyspnea, chills, or exposure to infectious diseases such as tuberculosis.   The patient had continued working since onset of symptoms.

Physical findings of significance, with the exception of a mild pharyngitis, were limited to the chest.   The left lower lobe of the chest revealed signs of pneumonic consolidation with possible effusion, and showed dullness to flatness, decrease in breath sounds, and tactile fremitus.   On September 30, 1948, three days after entry, the patient developed severe epistaxis, the temperature rose to 105° F., and râles were noted above the area of dullness in the left lower chest.   A white blood count at this time showed a total of 9,130 cells with normal distribution.   A roentgenogram of the chest taken on entry revealed an infiltration of the left hilar region and lower half of the left lung, consistent with pneumonia with effusion.   (Subsequent roentgen-

ray findings will be given at the end of the report.) A thoracentesis was performed at this time but, due to technical difficulties, only a small amount of fluid was removed. The fluid was amber in color and negative on smear and culture for bacteria, including acid fast bacilli. Routine agglutinations for typhoid, paratyphoid A and B, brucellosis, tularemia, and OX19, performed on September 30, 1948, were negative. The patient continued to run a septic temperature and, on October 4, 1948, signs of frank pleural effusion were elicited as high as the fifth rib posteriorly on the left side. A chest film of this date confirmed the physical findings. A white blood count on October 6, 1948, showed a total of 6,350 cells with a differential of 63 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, and 10 per cent monocytes; the sedimentation rate was 46 mm., corrected (Wintrobe). On October 8, 1948, it was noted that the patient had been afebrile for 48 hours, and a Mantoux test was done which was negative. On October 13, 1948, another thoracentesis was performed and 1,500 c.c. of amber colored fluid were removed from the left pleural cavity. The fluid was found to have a specific gravity of 1.045, and the stained sediment showed 91 per cent lymphocytes, 9 per cent polymorphonuclear leukocytes, and rare gram positive diplococcus; acid fast bacilli were not seen, and subsequently did not grow on culture. Repeated blood cultures were negative. A search for etiology of the pulmonary disease was started, and on October 14, 1948, a coccidioidin skin test in 1:100 dilution was negative. A white blood count on October 18, 1948, showed a total of 6,350 cells, with 66 per cent polymorphonuclear leukocytes, 29 per cent lymphocytes, 3 per cent eosinophiles, and 2 per cent monocytes. The patient was still running a low grade fever but had no specific complaints. On October 22, 1948, coincidental with subjective improvement, physical examinations revealed considerable clearing of the involved area. It is of interest that the patient received no antibiotic therapy. On November 8, 1948, more than one month after admission, a complement fixation test was positive for coccidioidomycosis in the sixth tube dilution, and subsequently a coccidioidin skin test was positive in the 1:10 dilution. On November 15, 1948, the patient having been afebrile for some time, was sent home on modified bed rest, to be followed in the out-patient clinic. He was seen at bimonthly intervals, and complete blood counts, complement fixation tests, and roentgenograms were done. On December 20, 1948, he still had some transient coarse râles in the left chest, but a roentgenogram revealed that the pleural effusion had entirely subsided. On December 29, 1948, the white count was normal in total number and distribution, and the sedimentation rate was 8 mm. corrected (Wintrobe). On March 2, 1949, the sedimentation rate was 28 mm. corrected, but two weeks later was normal. The complement fixation titers have started to drop and the patient is asymptomatic. It is felt that he should be followed until the complement fixation shows a marked drop in titer (see chart 1).

Roentgenograms. Films of *September 28, 1949,* seven days after onset of clinical symptoms: Vague clouding at the left base laterally, with an elevated diaphragm consistent with early pleurisy with effusion. Hazy thickening at the left hilum suggesting lymphadenopathy. *September 29:* Frank pleural effusion. The left hilum is partially obscured, suggesting glandular enlargement. *October 4:* Pleural effusion is now greater, with a marked cardiac shift to the right. The left hilum is completely obscured. *October 13:* Definite recession of the pleural fluid (following thoracentesis). The left hilum is partially clear but does not now give the appearance of lymphadenopathy. *November 8:* Further recession of the pleural exudate, with evidence of some plastic manifestation. *December 14:* Some residual pleural thickening at the left lower lateral thoracic margin and costophrenic sulcus. *January 21:* Slight recession of the pleural thickening near the left base. The left hilum remains hazily thickened. The lungs appear clear. *February 9:* There is no change in the pleural thickening. A very thin-walled ring shadow overlies the left lower hilar region. The
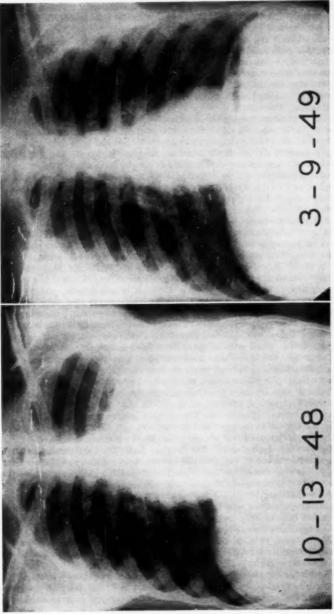
Fig. 1. *Case 1.* Massive pleural effusion which subsequently cleared almost completely leaving slight haze in left costo-phrenic sulcus.

left hilum remains indefinitely thickened.   *March 9*: The pleural thickening is receding definitely by this time. The left hilum remains hazily thickened. The ring shadow definitely persists and projects sufficiently beyond the hilum so that it must be considered parenchymal and one of the ring cavities so frequently seen in this disease. To summarize: there has been frank pleural effusion, with residual pleural thickening throughout; a suspicious haziness of the left hilum suggestive of lymphadenopathy. The latter conclusion is to be checked on subsequent films for the development of a parenchymal ring shadow. Throughout there has been no definitely proved parenchymal infiltration, although such might have been readily obscured by the overlying pleural effusion. Throughout there is a slight prominence near the base of the aorta but insufficient to identify lymphadenopathy.

Case 2. A 16 year old white male entered the hospital on September 29, 1948. The patient had lived in the vicinity of Los Angeles and had been committed 14 weeks earlier to a juvenile delinquency camp near Saugus, California, where he had been one of a crew on fire fighting detail. The camp physician's note accompanying the boy stated: "Upper respiratory infection with tracheobronchitis, fever, chest pain, muscle aches, and cough for two days, temperature 103° for one day." In the hospital a more complete history revealed that the patient first developed general weakness and malaise two days prior to entry, with a temperature elevation as high as 104° F. The next day he developed a sore throat and raw, substernal pain which was not influenced by respiration, change in position, etc. He also had anorexia and nausea. There was no history of cough or sputum, insect bites, eruption, or lymphadenopathy.

Physical examination on entry revealed an acutely ill white male with a temperature of 102.2° F., pulse 104 and blood pressure of 130/76 mm. Hg. His pharynx was slightly injected and he exhibited slight nuchal rigidity. There was a generalized lymphadenopathy of minimal proportions with soft submandibular, posterior cervical and axillary nodes, non-tender and none greater than 1 cm. in diameter. The physical examination of the chest was negative, and it was noted the patient produced a minimal amount of yellow sputum. A white blood count showed a total number within normal limits, with normal distribution of cells; on stained smear, some lymphocytes looked abnormal. A provisional diagnosis of fever of undetermined etiology was made and procedures were started to rule out influenzal syndrome, infectious mononucleosis, Q fever, brucellosis, and atypical pneumonia. On September 29, 1948, a coccidioidin skin test was positive in the 1 : 100 dilution. Various laboratory procedures were repeatedly run, including heterophil agglutinations, and routine agglutinations for typhoid, paratyphoid A and B, brucellosis, tularemia, and the OX 19 group. These were all negative. Complement fixation tests for coccidioidomycosis were run and were always negative. A Mantoux test with PPD No. 1 and No. 2 was done and was negative. A repeat white blood count again showed lymphocytes suggesting Downey Type I cells. On October 13, 1948, a differential count of the white blood cells showed 67 per cent polymorphonuclear leukocytes, 22 per cent lymphocytes, 13 per cent monocytes, and 8 per cent eosinophiles. Roentgenograms of the chest revealed right paratracheal adenopathy, especially when compared with a film taken three months previously. Numerous sputa and gastric washings were negative for coccidioidomycosis and acid fast bacilli, both on direct smear and on culture. As the patient had been afebrile and asymptomatic since five days after entry, it was felt safe to send him home on modified bed rest on October 17, 1948.

On November 8, 1948, he was seen in clinic and had remained asymptomatic and afebrile, with a satisfactory weight increase. Mediastinal lymphadenopathy was still present on roentgenogram.

On November 20, 1948, he complained of an upper respiratory infection and his temperature was 99.4° F. The white blood count was 18,000, with 68 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes, 12 per cent monocytes, and 4

per cent eosinophiles.   A complement fixation test for coccidioidomycosis was nega-
tive.   He entered the hospital again on November 23, 1948, but remained afebrile and
asymptomatic.   Sputa and gastric washings were repeated and were always negative.
He was sent home one week after entry.   On November 22, 1948, a chest roent-
genogram showed marked regression of the right paratracheal lymphadenopathy.

   Roentgenograms: The first film, on *September 30, 1948,* four days after onset, re-
vealed a typical right upper mediastinal broadening consistent with enlargement of
the right paratracheal glands; otherwise the roentgenogram was not remarkable
except for a local distortion of direction over one of the truncal structures passing
from the right second interspace zone to the hilum with some thickening.   *October 1:*
Questionable increase in the right paratracheal enlargement; otherwise unchanged.
November 22: Sharp regression of the right paratracheal mass so that residual lymph-
adenopathy at this time would be difficult to recognize, except that it can be identified
in comparison with the previous miniature chest film of July 7, 1948, which revealed
a normal upper mediastinum.   The essentials are obviously right paratracheal lymph-
adenopathy which slowly receded without positive evidence of an associated paren-
chymal lesion.

   Case 3.   This 16 year old white male entered the Los Angeles County General
Hospital on November 14, 1948.   The patient was one of a group of boys at a forestry
camp and was being followed by monthly complement fixation tests for coccidioido-
mycosis.   The past history revealed that he had been born in Maryland, had spent
many years in Los Angeles, and had never been in the San Joaquin Valley or any
other known endemic area for coccidioidomycosis.

   On November 14, 1948, the patient noted the onset of severe headache and stiff
neck.   He was found to be febrile and was sent to the Contagious Disease Unit of
the Los Angeles County General Hospital to rule out meningitis.   The physical ex-
amination at this time revealed a temperature of 101.2° F. and pulse of 80; the res-
piration was 20.   The remainder of the examination was essentially negative except
for the presence of slight nuchal rigidity and some hyperemia of the right tympanic
membrane.   The neurologic examination showed no abnormalities but because of a
poliomyelitis epidemic at the time a lumbar puncture was done.   It revealed normal
dynamics.   The fluid contained 2 lymphocytes, a negative Pandy, the sugar qualita-
tively normal, and there was no growth on culture.   A white blood count revealed
a total of 9,700 cells, with a normal distribution.   The patient was discharged with a
diagnosis of "upper respiratory infection."   Since this patient was one of a group
which we had been investigating, and since his complement fixation titer for coc-
cidioidomycosis had climbed considerably in the past month, it was felt that further
hospitalization and investigation were warranted before permitting his return to active
work.   He was brought back to the main unit of the hospital on November 26, 1948.
His examination was entirely negative except for a minimally productive cough, and
he remained symptom-free during his entire hospital stay.   On November 29, 1948, a
lumbar puncture revealed normal dynamics and normal fluid.   The blood showed
normal hemoglobin and erythrocyte count, and the white blood cells numbered 8,200,
with a normal distribution.   Complement fixation for coccidioidomycosis was per-
formed and may be seen in chart 1.   It was elevated.   The chest roentgenogram
was normal.   On December 7, 1948, a gastric washing (one of five such tests) re-
vealed spherules typical of *Coccidioides immitis* on direct mount.   All other sputum
specimens and gastric washings were entirely negative for this fungus.   On January
3, 1949, the sedimentation rate was three millimeters corrected (Wintrobe), and the
white blood count was 6,000.   The patient was discharged to a modified bed rest
regime at home, although he still had a moderately high complement fixation titer.
On February 7, 1949, it was noted that the complement fixation for coccidioidomycosis
had dropped in titer.

Roentgenograms: Three films were obtained: one on *November 10, 1948,* for acute respiratory symptoms; one on *November 30, 1948,* and one on *January 3, 1949,* after onset of respiratory symptoms. All films were practically identical, showing no trustworthy evidence of disease. Another film on *January 21, 1949,* was also negative.

Case. 4. The patient was a 16 year old white male of Mexican ancestry who was born in Texas and who had lived in Los Angeles for a considerable length of time. He had been working at the camp previously described. The note accompanying the patient stated: "Bronchopneumonia—had chest pain, fever, cough for three days, and a febrile illness during the week prior to the present illness."

The patient entered the Los Angeles General Hospital on September 28, 1948, and a history at that time revealed that six days prior to entry he developed slight fever, malaise, anorexia, and dull substernal pain. He then spent a few days in bed and felt a little better for two days, but previous symptoms returned with increased severity. In addition, he developed a cough productive of a moderate amount of yellowish sputum. Physical examination showed an acutely ill boy with a temperature of 102.3° F., a pulse of 100, and a respiratory rate of 20. He had a mild conjunctivitis and pharyngitis. His neck was supple, lungs were clear to percussion and auscultation, and he showed a generalized lymphadenopathy, with the submandibular and anterior and posterior cervical nodes being most prominent. The remainder of the examination, including the neurologic, was negative. A provisional diagnosis of primary atypical pneumonia was made, with acute coccidioidomycosis, infectious mononucleosis and Q fever as distinct possibilities. On the day of admission, a complete blood count showed a hemoglobin of 15.5 gm. and a white blood count of 14,200, with 64 per cent polymorphonuclear leukocytes, 28 per cent lymphocytes, and 8 per cent eosinophiles. The patient ran a febrile course varying from 99° to 101.5° F. until October 7, 1948, and thereafter was afebrile and asymptomatic during his entire hospital stay. His therapy was entirely symptomatic and no antibiotics were given. A number of laboratory examinations were performed and all were negative. These included heterophile antibody (repeated three time) and the routine agglutinations given above, cold agglutinins, Q fever agglutinations, and throat smear. On September 29, 1948, a coccidioidin skin test in 1:100 dilution was read as *negative.* On October 4, 1948, a PPD No. 1 was negative. Repeated white cell counts showed two things of note: a number of atypical lymphocytes (suggestive of Downey Type I cells), and an eosinophilia which ranged as high as 11 per cent. On October 18, 1948, his coccidioidomycosis complement fixation test was reported as positive in the sixth tube dilution and subsequently continued positive (see chart 1). Radiographic findings in the left upper lobe were present on the day of admission and continued to date (see below). On November 8, 1948, a coccidioidin skin test in 1:10 dilution was strongly positive, but was negative in the 1:100 dilution. The patient was discharged home to modified bed rest shortly thereafter and was followed in the clinic at bimonthly intervals.

The patient remained completely asymptomatic at home and gained some weight. On February 9, 1949, a routine white blood count revealed an eosinophilia of 6 per cent. The sedimentation rate on the same date was 5 mm. corrected (Wintrobe). The complement fixation, while not positive in as high a titer as previously, was still positive. At this time the possibility of osseous dissemination was raised. On March 2, 1949, the white blood count was 7,950, with an eosinophilia of 1 per cent, and the sedimentation rate was 10 mm. corrected (Wintrobe).

Roentgenograms: The chest film of *September 29, 1948,* seven days after onset, was read as follows: confluent infiltration above the left second interspace, deepening to consolidation at the level of the clavicle, and a mediastinal protrusion at the left hilar level indicative of glandular enlargement. Some scattered involvement as low as the third rib was also noted. *October 1:* Slight clearing of the parenchymal in-
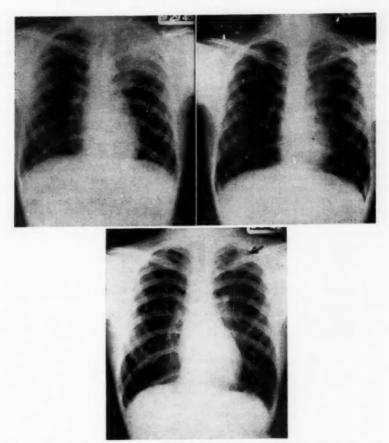
Fig. 2. *Case 4*. Note rapid clearing of consolidated area in left apical region. On lower plate arrow indicates suspected osseous involvement.

filtration is noticed, but there is an increase of the lymph gland enlargement. *October 19:* There is definite progress in resolution of the involvement of the left upper lobe, leaving scattered mottled involvement above the second rib. The lymphadenopathy appears stationary. *November 8:* There is slight further regression of the pulmonary involvement and partial regression of the lymphadenopathy. *February 9:* There is still more slight regression of the parenchymal involvement. The left hilar lymphadenopathy is no longer clearly evident. On the films of *October 9, November 8,* and *February 9*, there is an appearance of rarefaction in the left first rib, somewhat difficult to distinguish between an osseous lesion and a small excavation in the underlying lung, but, because of identical location with relation to the rib on the films showing slightly different centering, it is presumably an osseous lesion.

Case 5. The patient was an 18 year old white male who was born and who had

lived in Los Angeles all of his life except for the years from 1935–37, during which time he had resided in Iowa. This patient, one of a group who had been working in the aforementioned forestry camp, entered the Los Angeles County General Hospital on September 28, 1948. At the time of entry the history revealed that he had developed a severe type of pounding headache five days previously, and the next day a temperature of 102° F. was noted. That night he developed chest pain in the anterior lower chest and aches in his leg muscles, and had a severe, bed-shaking chill. On the day prior to admission he had one episode of epistaxis.

The physical examination revealed a moderately ill young man with a temperature of 101.8° F., minimal pharyngeal injection, a generalized lymphadenopathy with small succulent nodes in the cervical and post cervical, axillary, and inguinal regions. Although the liver and spleen were not palpable, the patient admitted to moderate tenderness in the right upper quadrant. The remainder of the examination, including heart, lungs, and neurological, showed no findings of note. A provisional diagnosis of infectious mononucleosis was made, with atypical pneumonia, coccidioidomycosis, Q fever, and influenzal syndrome to be considered. Laboratory work on the day of admission showed a negative urine, a hemoglobin of 17 gm., a red blood cell count of 5,400,000, a white blood cell count of 11,000, with 76 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes (many with peculiar morphology), 4 per cent monocytes, and a sedimentation rate of 26 mm. corrected (Wintrobe). The patient continued relatively asymptomatic with a minimally febrile course for one week, with the temperature ranging from 99° to 101° F. He was treated symptomatically and was not given antibiotics. Numerous laboratory examinations were conducted and all were negative. These included heterophile agglutinations (repeated three times), throat culture, thymol turbidity, cephalin flocculation, routine agglutinations mentioned previously, and cold agglutinins.

On October 5, 1948, a hemogram showed a white blood count of 6,850, with 40 per cent polymorphonuclear leukocytes, 40 per cent lymphocytes (many were similar to Downey Type I cells), 12 per cent monocytes, 6 per cent eosinophiles, and 2 per cent basophiles. On October 7, 1948, a coccidioidin skin test was positive, and on October 18, 1948, the complement fixation test for coccidioidomycosis was positive in the third tube. For further data on the complement fixation test see chart 1. A chest roentgenogram on admission showed infiltration in the right upper lobe; subsequent readings are given below. Since the patient had been afebrile and asymptomatic for some time, and since the sedimentation rate was normal, he was discharged to home on modified bed rest on October 25, 1948, and followed in the clinic at bimonthly intervals.

The patient gained weight, remained asymptomatic and, on February 9, 1949, showed a remarkable decrease in his complement fixation titer. At this time the white blood count was entirely normal, with a 2 per cent eosinophilia, and the sedimentation rate was 4 mm. corrected (Wintrobe). On March 2, 1949, the white blood count was still within normal limits, and the sedimentation rate was 3 mm. corrected (Wintrobe). The patient was discharged from further observation.

Roentgenograms: The first film, on *September 29, 1948,* seven days after onset: There are a zone of cloudy infiltration in the right subapex, a frank enlargement of the right paratracheal glands, and a suspicious blunting in the aortic knob suggestive of partially concealed glands in that region. *October 14:* There is slight but very incomplete resolution of the infiltration and a slight decrease in the glandular enlargement. *February 9:* There is marked but still incomplete resolution of the infiltration leaving a hazy nodose shadow. The lymphadenopathy is no longer visible.

Case 6. The patient was a 17 year old white male who was born in Colorado, had lived in Los Angeles for a number of years, and was one of a group of boys being followed in a forestry camp. It was noted on serial complement fixation tests
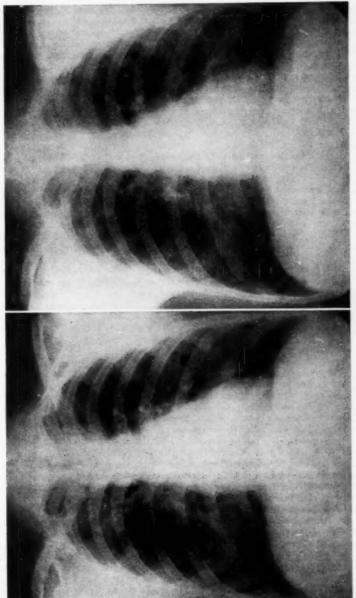
Fig. 3. Case 5. Exhibits both right subapical infiltration and right paratracheal lymphadenopathy. Adenopathy subsided completely, some infiltration remains.

for coccidioidomycosis that his titer was rising and, on December 20, 1948, he was found in bed complaining of cough, lassitude, fatigue, weakness and a fever. It was felt that he should be hospitalized for a more extensive work-up, and he was admitted to the Los Angeles County General Hospital the next day. A detailed history obtained in the hospital revealed that this patient was ill three months ago, at approximately the same time that the first boys—Cases 2, 4, and 5— were seen. His symptoms consisted of a rhinitis followed by a sore throat, cough, a low grade febrile response, and malaise. This acute episode lasted for one week, after which the patient returned to work with a persistent cough and malaise. These symptoms, combined with anorexia, have continued to the present time. One week prior to entry he developed a rather severe headache, stiffness of the neck, and mild backaches, which had abated by the time of entry. Friends stated that the patient looked quite unwell and seemed tired all the time.

On physical examination the patient appeared pale, listless, and lethargic. His temperature was normal. A moderate pharyngitis was noted with small soft cervical nodes bilaterally. The remainder of the examination, including heart, lungs, and neurological, was within normal limits. A provisional diagnosis of possible primary pulmonary coccidioidomycosis was made, and the patient was placed on bed rest. He displayed no symptoms except the aforementioned lethargy. This disappeared in one week, and he was symptom-free and afebrile for the rest of his hospital stay.

On entry a routine blood count showed a hemoglobin of 14 gm., a white blood count of 7,600, and a normal differential count. A lumbar puncture, performed on November 22, 1948, revealed normal dynamics and the other spinal fluid findings were within normal limits. Culture was negative. A repeat hemogram showed 8,150 white cells, with 53 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes, 5 per cent monocytes, 5 per cent eosinophiles, and 1 per cent basophiles. Heterophil antibody was negative, and previously stated routine agglutinations were likewise negative. A chest roentgenogram on December 22, 1948, was read as essentially negative. The sedimentation rate was 6 mm. corrected (Wintrobe) on December 30, 1948.

Repeated gastric washings and sputum examinations failed to reveal any organisms of *Coccidioides immitis*, either on direct mount or culture, yet his complement fixation titer remained high. On January 5, 1949, the complement fixation titer had started to drop, and the sedimentation rate was 0 mm., so the patient was sent home to modified bed rest to be subsequently followed in the clinic. At no time did he develop any symptoms, and the laboratory findings were either normal or nearly normal. On January 24, 1949, a minimal strand lesion appeared in the left apex on roentgenogram but receded on February 9, 1949.

Roentgenograms: The film of *November 10, 1948*, a survey film before onset of symptoms, is negative. *December 23, January 24*, and *February 9:* There are strand appearances toward the left apex, most advanced on the film of *January 24*, and receding on the one of *February 9*. In retrospect, no definite finding is evident on the original film. The films are otherwise negative, without evidence of frank lymphadenopathy or of diffuse parenchymal infiltration.

Case 7. This is a 19 year old white male who was born and had lived in Brea, California. He had been working at a forestry camp (see before) for two to three months prior to entry.

Counselors at the camp stated that he had been ill one month prior to the present episode with an upper respiratory infection. However, because he was a moody, introspective boy and did not complain, he was permitted full activity. On October 21, 1948, he developed a severe frontal headache, felt feverish and was sent into Los Angeles to a county medical dispensary. He was observed for seven days, during which time he complained of headache and ran a minimally febrile course, although

on one occasion his temperature rose as high as 104° F.   On the day of entry, October 28, 1948, he vomited once and complained of headache and stiff neck, and was therefore admitted to the Contagious Disease Unit of the Los Angeles County General Hospital as a poliomyelitis suspect.   A Mantoux test was positive on October 25, 1948.

The history taken in the hospital on admission revealed a weight loss for the past two to three months, and headaches and night sweats for the past two to three weeks. The temperature was 99.6° F. and the pulse 95.   The lungs had coarse transient rhonchi throughout; the neurologic examination was negative, and routine laboratory
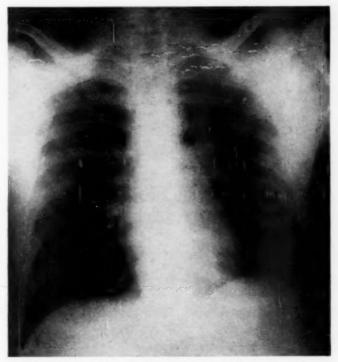
Fɪɢ. 4.   *Case 7.*   Fatal case of meningitis with right paratracheal lymphadenopathy.   On autopsy, lesion was found in right lower lobe.   Not detected by roentgenogram.

work showed normal hemoglobin, a total white count of 6,250 cells with a normal distribution, and a sedimentation rate of 7.5 mm. corrected (Wintrobe).   A lumbar puncture showed normal dynamics, with a negative spinal fluid containing a rare lymphocyte and 11 mg. per cent protein.   A provisional diagnosis of possible pulmonary tuberculosis was made.   Fluid obtained by gastric lavage of this date proved negative on subsequent culture for bacteria, including acid-fact bacilli.   A roentgenogram of the chest (figure 4), taken on October 29, 1948, revealed questionable right paratracheal adenopathy but nothing else.

The patient became irrational on November 2, 1948, and a repeat lumbar puncture

revealed 864 lymphocytes, 191 mg. per cent protein, and a negative smear and culture for bacteria and acid-fast bacilli. At this time, because of the history of coccidioido-mycosis at his camp, the patient was skin tested with coccidioidin in 1 : 100 dilution, and this was read as 3-plus positive. On November 4, 1948, he felt better but was irritable. On this date the spinal fluid revealed spherules, the chlorides were 632 mg. per cent, and total protein 242 mg. per cent. Complement fixation for coccidioido-mycosis was reported positive on the blood drawn on November 8, 1948, in high dilution, and also positive in the spinal fluid on December 1, 1948 (see chart 1). On December 2, 1948, cultures from spinal fluid drawn one month earlier had grown
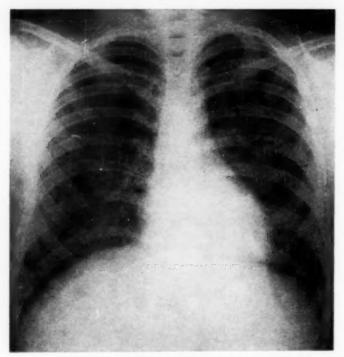
FIG. 5. *Case 8*. Non-hospitalized patient with thin-walled cavity in left hilus, found on routine roentgenogram. Asymptomatic.

Coccidioides immitis. The patient continued to be surly and uncoöperative. He was remarkably free of symptoms and showed no physical findings. Colloidal copper injections, given 4 c.c. intramuscularly two times weekly, showed no effect as evi-denced by spinal fluid and complement fixation changes. He was transferred to a medical service on December 2, 1948. A complete physical examination, including funduscopic and neurological, revealed little, if any, abnormality. Because of the patient's surly attitude, a psychiatric examination was obtained and a diagnosis of schizoid personality was made. On December 7, 1948, a complete neurological examination was made and revealed a slightly hyperactive left knee jerk. There

were no localizing signs or evidence of motor or sensory aberration. On December 29, 1948, it was noted for the first time that his spinal fluid sugar had dropped to 34 mg. per cent. A repeat neurological examination on January 1, 1949, revealed some blurring of the disc margins of both fundi without signs of hemorrhage. There was a rapid coarse tremor of both hands and questionable extensor weakness of the right lower extremity. The Oppenheim and Babinski signs were positive on the right, and the left knee jerk was hyperactive.

He was given Jacobson's antigen, and 24 hours after the injection had a chill; no more was given. The patient then received 10 c.c. of immune globulin with no effect. Since the patient wished very much to go home, and since it was felt that little if anything could be done for him at the hospital, he was permitted to go home to full bed rest on January 28, 1949.

CASE 7, Spinal Fluids

Date	Appearance	Cells	Culture	Pandy	Sugar	Chlorides	Protein	Comp. Fix.
10/29*	Sl. ground glass	Rare lympho.	Neg. bact.				11 mg.%	
11/2	Sl. cloudy; ground glass	864 lymphos. AFB smear neg.	Neg. bact.	+ +			191 mg.%	
11/3*	Ground glass, colorless	Many lymphos. No fungi or AFB seen	Neg. bact.	+ + +		632 mg.%	242 mg.%	Positive
11/4	Ground glass	420; 92% lymphos. Spherules like yeast, 5 micra in diameter	Coccidioides immitis	+ + +	Red.			Positive
11/9	Ground glass	720; 90% lymphos. No spherules seen	Coccidioides immitis	+ + +	Red.		263 mg.%	Positive
11/12	Clear	257; 80% lymphos.	Coccidioides immitis	+	Red.			Positive
11/30	Clear	396; 80% lymphos.	Coccidioides immitis	+	Red.			Positive
12/7	Ground glass	400; 85% lymphos. Double contour spherules	Coccidioides immitis AFB neg.	+ + + +	60 mg.%	600 mg.%	210 mg.%	Positive
12/29	Ground glass	379; 80% lymphos.	Coccidioides immitis	+ + + +	34 mg.%	632 mg.%	200 mg.%	Positive
3/2†	Xanthochromic; clear	8 large lymphos. or monocytes; no spherules	Coccidioides immitis	+ + +				Positive

* A small pellicle formed on standing.
† Dynamics; Initial pressure of 60 mm. of water: block on the right side: good rise and fall on the left.

The patient reentered the hospital on February 19, 1949, and his condition had markedly deteriorated. Since discharge he had developed marked weakness of the upper extremities, numbness and tingling of the hands, and pain in the right side of the neck. He had bouts of vomiting and one transient episode of weakness of his legs one week prior to entry. A neurologic consultation revealed choked discs, hemorrhages and macular exudates bilaterally. Nystagmus was noted in all planes. There was some weakness of the trapezius on the right, while both upper extremities exhibited a flaccid paresis, although the fingers could be moved slightly. The legs had fair motor power, and there were no pathological toe signs. There was hyperesthesia of the hands up to the mid-arms. The position sense was poor in the legs, and deep pain was diminished. Neurological diagnosis: The patient had signs of an obstructive lesion of the cerebrospinal fluid circulation, plus compression of the cord at about the level of the cervical enlargement. This was probably due to arachnoiditis, both of the basilar portions and of the upper cervical spinal cord.

By February 28, 1949, it was noted that the patient now had a complete flaccid paralysis of both upper extremities and was regurgitating fluids. On March 2, 1949, marked weakness of both lower extremities developed, and the coccidioidin skin test

was positive in 1:100 dilution but diminished in size. He was afebrile most of the time but steadily deteriorating, and on March 25, 1949, developed urinary incontinence. He died on April 11, 1949. An autopsy proved the diagnosis and will be discussed in detail in a later publication.

Roentgenograms: Films were taken on *October 29, 1948,* and *November 10, 1948.* The first, taken one month after the onset of the respiratory infection, reveals only small glandular enlargement in the right paratracheal region and a questionable one at the left hilum.

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ERRORS IN DIAGNOSIS AND MANAGEMENT OF CANCER *

PART II

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II. Advanced Inoperable Cancer Was Diagnosed—Operable Cancer Was Found

This group consists of five cases as shown in table 2.

Case 12. A 39 year old male was admitted to Montefiore Hospital in October, 1946, with a complicated history and a seemingly hopeless prognosis. His illness began in July of 1945, with sudden onset of fever which reached 104° a few hours after he had received an injection of a sclerosing agent into the hemorrhoidal areas. This fever persisted for two weeks and recurred intermittently. At first no definite diagnosis was established as there were no localizing signs present. Six months later there was a sudden onset of severe pain in the right thigh, which was interpreted as neuritis and was treated unsuccessfully with prostigmine and parenteral vitamins. There was gradual weight loss, spiking fever, general malaise, and the development of a mass. For these complaints he was admitted to another hospital in July, 1946, and a 15 cm., smooth, mobile and tender mass was felt on deep palpation adjacent to a well healed appendectomy scar. Barium-meal examination showed the upper gastro-intestinal tract to be normal. Barium enema revealed evidence of extrinsic pressure on the ascending colon; excretory urography was negative.

Neurologic examination revealed atrophy of the right hamstring and extensor muscles with decreased motor power, hypalgesia, and hypesthesia of the medial aspect of the right calf. The right knee jerk was absent. These findings were interpreted as "neuropathy" involving the segments from L-1 to L-4. Absence of the right testicle was noted. Patient's temperature rose daily, reaching 104° F.; sedimentation rate was excessive—115 mm. per hour. The blood count was normal; urine was negative. The palpable mass was aspirated and the specimen described as fragments of a "highly malignant spindle cell sarcoma." In view of the neurologic findings assumed to represent a widespread infiltrative process and the result of the tissue examination, exploratory laparotomy was deemed inadvisable and radiotherapy was given. The mass shrank somewhat. After completion of the diagnostic and thera-peutic procedures, the patient was sent to this hospital "for chronic hospitalization."

On admission to Montefiore Hospital in October, 1946, the patient was completely bedridden and emaciated, weighing 79 pounds. He had lost 91 pounds during his period of illness. Blood pressure was 112/74 mm. Hg; pulse, 130. The temperature ranged between 100° F. in the morning and 104° F. in the evening. The heart was enlarged to the left with a blowing systolic apical murmur. Lungs were negative.

A deep seated mass, as previously noted, was felt in the right lower quadrant. Liver and spleen were not enlarged. The right testicle was not felt. No significant lymph nodes were found.

Neurologic examination revealed considerable progression; a bilateral foot-drop was almost complete on the right and marked on the left. There was marked weakness of all the muscles of the right lower extremity, and weakness of vibration sense over the right lower extremity was noted. These findings were interpreted as pressure effects upon the right lumbosacral plexus and nutritional deficiency neuritis accounting for bilateral involvement. Ophthalmoscopic examination revealed bilateral hemorrhages and exudates. Laboratory tests showed 5.5 gm. hemoglobin, 1,670,000 red cells, and 8,100 white cells, with 76 per cent neutrophiles. Bone marrow studies were negative. The urine contained traces of albumin, the sediment a few red cells and granular casts. Blood cultures were negative. Friedman test was negative.

TABLE II

Case No.	On Admission	Final	Error
12	Retroperitoneal spindle cell sarcoma with invasion of lumbosacral plexus.	Encapsulated malignant tumor in undescended testicle.	Interpretation of physical findings. No surgical exploration.
13	Carcinoma of rectum with pulmonary and osseous metastases.	Primary lung carcinoma. Benign rectal polyp. Healed compression fracture.	Microscopic interpretation. Roentgen-ray interpretation.
14	Carcinoma of rectum, with invasion of bladder neck and urethra.	Carcinoma of rectum, no extension, no metastasis.	Surgical gross findings.
15	Carcinoma of ascending colon with invasion of mesentery.	Carcinoma of ascending colon without extension.	Surgical gross findings.
16	Carcinoma of sigmoid with perforation and spread.	Carcinoma of sigmoid.	Surgical gross findings.

In preparation for exploratory laparotomy the patient was treated with high doses of parenteral vitamins, penicillin, intravenous infusions of protein hydrolysates, and repeated blood transfusions. During this preparation he became jaundiced. In spite of this, exploration was carried out and a completely encapsulated large oval mass situated in the right retroperitoneal space, measuring 16 by 11 by 11 cm. and weighing 950 gm., was removed with relative ease (see figure 8). The tumor was extremely necrotic and freshly hemorrhagic; a definite microscopic diagnosis was impossible. Several gross and microscopic features were strongly suggestive of a testicular neoplasm.

The patient's postoperative recovery was dramatic. He became afebrile within 24 hours, the pulse rate dropped, the appetite improved, and he gained weight at an amazingly rapid rate. The severe anemia disappeared. Physiotherapy was instituted. He became ambulatory, was able to walk without the aid of a cane, and returned to work. He regained his full weight. Follow-up 18 months postoperatively revealed the patient to be in good condition and asymptomatic. Roentgen-ray studies of the chest demonstrated a round density in the right lower lobe. Other metastases, including spread to the brain and both lungs, followed quickly. There was rapid deterioration and the patient died in July of 1948, 21 months postoperatively. Autopsy confirmed the clinical findings. Histopathology was fibrosarcoma.

Fig. 8. *Case 12.* Surgical specimen—tumor of ectopic testicle.

The high incidence of malignancy occurring in cryptorchidism is well known. Therefore, a retroperitoneal mass on the side of an undescended testicle led us to assume that we were dealing with a malignant ectopic testicular tumor. The surgical management was in logical sequence to the diagnostic reasoning, which did not change the diagnosis of malignancy but altered the estimate of operability. The jaundice, which occurred pre-

operatively and was hemolytic in type, was probably caused by the massive fresh hemorrhage found in the tumor.

Surgery was unable to cure this patient; in spite of its long delay, however, it did help the patient to regain his strength fully and to restore him to a normal life for a period of at least one and one-half years.

Case 13. A 58 year old male was referred to Montefiore Hospital in July, 1948, from a large midwestern city with the diagnosis of carcinoma of the rectum with pulmonary and osseous metastases. The purpose of his referral was to attempt to influence his "hopeless and advanced condition" (of which he was aware) by some chemotherapeutic experimentation. His present illness began in January of the same year with fever, cough, rusty sputum, and general weakness. He was kept in bed for three weeks and was treated with penicillin and sulfonamides. The fever subsided; the cough and general malaise persisted. Chest roentgen-ray revealed a "consolidated area the size of a walnut in the fourth interspace anteriorly on the right, which is probably postpneumonic residue." Weakness and cough continued, and he began to complain about the intermittent appearance of black-clotted blood in the stool, which was occasionally tinged with fresh blood. In mid-March, roentgen-ray examination of the chest revealed the previously noted area of consolidation and signs of emphysema. In mid-April, sigmoidoscopy was performed. At 10 cm. above the anal margin, on the anterior rectal wall, a smooth 7 mm. polyp was seen and biopsied. The specimen was reported as adenocarcinoma of the rectum, grade 2, which "does not as yet show very extensive penetration." In April he was admitted to a hospital for further study. Bronchoscopy was performed, which was negative. In the sputum malignant cells were found, being identified as adenocarcinoma. A roentgen-ray of the lumbar spine was read as extensive osteoclastic metastasis to the fifth lumbar vertebra with some compression of the body. However, there was a history of an old injury. He was discharged from the hospital as inoperable. He was then seen at a clinic, where films were reviewed and the patient released. The injury of the lumbar spine referred to above occurred about 30 years ago; there was no subsequent disability.

On admission to Montefiore Hospital in July, 1948, the patient was in fair general condition and showed no evidence of weight loss. There was a slight dullness to percussion on the right infraclavicular area, with a few wheezes. The remainder of the physical examination was noncontributory. Blood count and blood sedimentation rate, urine, and temperature were within normal limits. On sigmoidoscopy at the same area as previously noted, a grossly benign-appearing polyp, about 4 mm. long on a base about 4 mm. broad, was noted and removed at the base. The histologic diagnosis read: "Head of adenomatous polyp." The slides from the previous biopsy of the rectal polyp and from bronchial aspirate were reviewed by our pathologist. The former was interpreted to be an adenomatous polyp, the latter as "bronchial lining cells . . . none are well enough preserved or sufficiently atypical to warrant a diagnosis of tumor cells." Chest films revealed a round density about 3.5 cm. in diameter located in the basal portion of the right upper lobe (figure 9). Comparison of this density with earlier films showed concentric growth over a period of four months. Roentgenograms of the lumbosacral spine showed moderate bone atrophy and marked osteoarthritic changes, lipping, and partial bridging. The bridging between the vertebrae appeared to be complete on the right between L–4 and L–5. Marked osteoarthritic changes were seen between the inferior articulations of L–4 and superior articulations of L–5. The body of L–5 was considerably narrowed cephalocaudally and widened in its anteroposterior diameter. The posterior portion of the body encroached upon the vertebral canal. The appearance of the fifth lumbar vertebra sug-
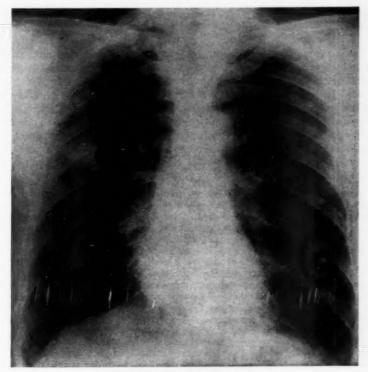
FIG. 9. *Case 13.* Chest film showing round density in right upper lobe.

gested old changes due to a healed compression fracture. The patient was rebroncho-scoped and again no endobronchial masses were seen. Bronchial secretion was aspirated from the right upper lobe, stained after the Papanicolau technic, and the material so obtained was studied with the conclusion "probable tumor cells present."

The diagnosis was now changed to primary lung carcinoma, with benign rectal polyp, osteoarthritis, and old-healed compression fracture of fifth lumbar vertebra. Thoracotomy was performed and a circumscribed tumor at the base and periphery of right upper lobe was found; there was no node involvement and the tumor was re-moved. Marked emphysema and anthracosis were also present. The surgical speci-men on histologic examination was judged to represent an "anaplastic carcinoma with foci of papillary adenocarcinomatous differentiation." The patient made a fairly uneventful recovery and was discharged three weeks postoperatively.

This case history illustrates a number of important diagnostic points: A lung tumor frequently simulates the clinical course of upper respiratory infections and pneumonia. While one may suspect that a growing and dense roentgen-ray shadow in the lung may represent malignant tumor, the decision to explore will depend on whether one considers this as primary or

secondary growth. The differential diagnosis between solitary metastatic lung nodule (though rare in the course of gastrointestinal malignancy) and primary carcinoma is at times very difficult. Metastatic tumors are known to break through larger bronchi and can well reproduce the clinical and bronchoscopic findings of a primary lung cancer. The differential diagnosis is greatly simplified if another primary focus or other organ metastases are found. In this patient's case, a benign rectal adenoma was histologically misinterpreted. Roentgen-ray findings of a compression fracture of a lumbar vertebra were read as osteoclastic metastasis, and this completed the picture of an inoperable rectal cancer with lung and spine metastases. It is of interest to point out that the same histologic section of the polyp and the same slide of bronchial aspirate were interpreted differently by two pathologists.

Case 14. This 62 year old male was admitted to Montefiore Hospital in June, 1946, with a diagnosis of inoperable carcinoma of the rectum. Two months before, this patient had been admitted to another hospital because of constipation, bloody stools, and severe rectal pain of about four months' duration. Examination at that time revealed a hard, constricting mass in the rectum. There was no clinical evidence of metastases. Cystoscopy revealed a mild encroachment of a median bar on the bladder neck. He was explored and the tumor was judged to have invaded the bladder neck and urethra. As a result of this gross impression, the idea of performing a combined abdomino-perineal resection "was abandoned." A loop colostomy in the descending colon was constructed. Following an uneventful postoperative course, he was discharged to await "appointment for terminal care at Montefiore Hospital." In the meantime he was admitted to another hospital where, because of pain, analgesics were given. There is no record of further investigation in that hospital.

On admission to Montefiore Hospital in June, 1946, the following were noted: functioning sigmoid colostomy; stenosing rectal tumor which was friable and cauliflower-like; evidence of tabes dorsalis with history of untreated neurosyphilis. The rectal tumor was found on sigmoidoscopy to be 2 inches above the anal orifice on the anterior wall not obstructing the lumen. A specimen of tissue removed for biopsy was reported as adenocarcinoma. Some of the examiners noted enlargement and nodularity of the liver, and there was evidence of impaired liver function. However, reëxploration was decided upon. A large, fungating tumor was found without evidence of intra-abdominal metastasis. There was no invasion of the bladder and urethra. The liver was found to be normal. Combined abdomino-perineal resection was performed, closing the distal limb of the loop sigmoidostomy. Examination of the surgical specimen revealed a tumor which had encircled the wall of the rectum completely but had not perforated through it. Lymph nodes from the perirectal fat showed only hyperplastic lymphadenitis. The patient died suddenly on his eighth postoperative day of generalized peritonitis caused by necrosis of the suture line closing the sigmoid at the site of resection. The autopsy showed no distant metastasis and confirmed our operative finding that the bladder and urethra were free of invasion.

A review of this case reveals that this patient, who had been declared inoperable on gross examination of the pelvic organs, had a distinctly operable lesion even three months later. The apparent extension of the tumor to the surrounding organs was probably inflammatory reaction which subsided following diversion of the fecal stream. Such patients should be reëvaluated after proximal colostomy.

Case 15. This 62 year old male was admitted to Montefiore Hospital in October, 1947, with a history of recurrent attacks of diarrhea and abdominal pain of seven months' duration. There was no blood in the stool. Weight loss of 20 pounds was reported. Three months earlier he had been admitted to another hospital with the same complaints, then of four months' duration. He was treated and subsequently discharged to a convalescent home on August 10. Upon request, we were informed by the hospital and the convalescent home that the patient was admitted July 9, 1947, with complaints of alternating constipation and diarrhea of eight to nine months' duration. Roentgenograms taken at that time were negative. Following this, other roentgenograms showed an obstruction of the bowel that required operation. The patient was admitted and an exploratory laparotomy was performed. Carcinoma of the colon was diagnosed and not considered removable. An ileosigmoidostomy was done. The patient had an uneventful recovery and signed out against advice August 10, 1947. He was admitted directly to a convalescent home with the clinical diagnosis of tumor of the colon. The findings on that day were "moderate cachexia (weight 140 pounds) ; blood pressure, 165/55 mm. Hg; heart, lungs, liver, and kidneys showed no pathological changes. The abdomen was very distended and tender, especially in the region below the umbilicus. At first he was ambulatory, but had been losing ground considerably. About 10 days ago morning nausea and vomiting, sometimes profuse, set in. At the same time the patient suffered from severe abdominal cramps and diarrhea, alternating with constipation. His sleep was disturbed. In the past week the patient had become so weak that in the last few days he was forced to lie in bed. His weight had dropped from 140 to 134 by September 18." From the convalescent home he again entered the hospital of origin and remained there until his admission by transfer to our hospital. Only symptomatic treatment, diet, and narcotics were given, and resection, although temporarily considered at the first operation, was not again contemplated.

The only pertinent finding on admission to Montefiore Hospital in October, 1947, was a huge mass in the right upper quadrant of the abdomen which was lobulated, hard, non-tender, and freely movable. There was no clinical or roentgen-ray evidence of distance metastasis, liver involvement, or ascites. There was a marked anemia ; hemoglobin, 8 gm.; red blood cells 2,670,000. There was a leukocytosis of 14,000 with many young forms, and an intermittent low grade fever. Roentgen-ray examination by means of barium enema demonstrated the presence of a well functioning ileosigmoidostomy. Barium was seen to enter the cecum from the ileum and to fill the entire colon, outlining a cauliflower-like mass in the area of the hepatic flexure. In view of the absence of evidence of metastasis, this patient was prepared for surgery by several blood transfusions and streptomycin orally. On November 25, four months after the first operation, exploration was done. "A mass the size of a baby's head was encountered at the hepatic flexure infiltrating the root of the mesentery." A hemicolectomy was performed, removing that portion of the mesentery believed to be infiltrated with tumor. The postoperative course was relatively smooth and the patient was subsequently discharged improved. In February, 1950, at follow-up, he was found to be in excellent health, free of local recurrence or distant metastasis, had gained 29 pounds, and was fully ambulatory.

The gross description and histologic studies of the surgical specimen warrant more detailed comment. A nodular, fungating, ulcerated neoplasm was found, narrowing the lumen of the colon and extending outward to thicken the wall, and penetrating into but not through the subserosal fat. The external circumference of the colon in the vicinity of the tumor was 17 cm. The thickness of the wall varied from 3 to 8 cm. The subserosal fat and attached mesentery contained numerous lymph nodes as large as 1 cm. in diameter ; some of these were firm and appeared to be partially or completely replaced by an opaque tumor.

This gross impression was not borne out by microscopic examination. Although numerous lymph nodes were examined, none was found to be infiltrated by tumor and all demonstrated chronic hyperplastic lymphadenitis secondary to a severe inflammatory reaction in the adenocarcinoma of the colon.

During this patient's brief illness, he was subjected to three admissions in two hospitals and had one admission to a convalescent home. Prior to his definitive surgery he was one of the many hopeless, abandoned cases treated with supportive measures and narcotics, and he was steadily deteriorating.

The difficulties encountered in attempts to judge correctly the extent of the lesion and the nature of the enlarged lymph nodes are well illustrated by this case history. In this case, infiltration of the root of the mesentery and an apparent infiltration of the lymph nodes described by the pathologist were incorrectly estimated on gross examination, and the correct diagnosis was established only when the histopathology was definitely recognized.

Case 16. On July 23, 1947, this 60 year old single female was admitted to a hospital with a two to three day history of severe right lower quadrant pain, nausea, vomiting, and fever. The abdomen was diffusely tender, most markedly in the right lower quadrant. Rebound tenderness was present. Urine was negative. The white count was elevated to 10,600. She was acutely ill, her temperature was 101° F. and her tongue was dry and coated. She was suspected of having acute appendicitis and was explored immediately after admission. At operation the appendix was found to be normal. An orange-sized firm mass of "carcinoma" was found in the pelvis, with the apparent primary tumor in the sigmoid, perforated and with a loop of jejunum attached. The jejunum was freed, drains were placed to the site of perforation, and a transverse colostomy was performed. The only available record of a tissue examination reads as follows: "Fragments of fat tissue showing acute purulent inflammation and granulation tissue formation; no tumor in the specimen submitted."

The patient was transferred to Montefiore Hospital for terminal care in August, 1947, where the following additional findings were noted: Fair general condition, no fever. There was no evidence of cardiorespiratory disease, and no lymphadenopathy; the liver was not enlarged, and there were no palpable masses in the abdomen. A hard mass was felt on digital examination of the rectum at the tip of the examiner's finger. On proctoscopic examination a highly vascular grayish mass, which proved to be adenocarcinoma, was seen four and one-half inches above the anal orifice. The urine and white count were normal. There was a moderate anemia. Electrocardiogram was normal. There was no roentgen-ray evidence of metastasis in the chest, humerus, pelvis, or skull. Bony abnormalities were consistent with Paget's disease, known to be present for several years. After several blood transfusions, high protein feedings, and oral and parenteral administration of streptomycin, resection of the tumor with primary anastomosis was carried out in October, 1947. The postoperative course was uneventful. Three weeks later the colostomy was closed extraperitoneally. Patient was discharged to our Home Care Department. She is in good condition, has gained weight, and at this time, nine months after the resection, is free of intestinal complaints.

The presenting signs and symptoms of this adenocarcinoma of the rectosigmoid were those of a perforated viscus. In the majority of cases, perforation is indicative of tumor growth through all the layers of the intestinal wall, with extension of the tumor into the surrounding tissues. It is there-

fore understandable that the findings at the first operation, with adhesion of the jejunum to the affected sigmoid colon, were interpreted as evidence of extensive tumor growth.   Even at gross inspection it was felt that the tumor had "broken through the wall into the adjacent fat, which is extremely thickened by tumor and fibrosis.   Within this area several scattered, round, firm nodules are noted, perhaps representing tumor-filled lymph nodes."   In contrast to this gross impression, the microscopic examination of the resected specimen revealed that "the abscess does not extend to the serosa.   Several lymph nodes, which are included, reveal chronic lymphadenitis but no tumor."   It is quite possible, therefore, that acute symptoms were caused by an inflammatory process rather than by a perforated cancer.   It is of significance that such an inflammatory process can simulate perforation, though, as proved in this instance, no such perforation was present and the tumor, well operable, did not extend beyond the subserosa.

Of these five patients two (Cases 12 and 14) died, and three are doing well (Cases 13, 15 and 16).   In the one (Case 12) distant metastases were found about 16 months postoperatively, and death followed in a few months.   For over one and one-half years, this young man, admitted for terminal care, lived a comfortable and productive life.   The second patient (Case 14) died because of postoperative complications.   In each of these five cases, misinterpretation of the pathology, either of the gross pathology in situ or of microscopy, was responsible for the delay in definitive treatment. In Case 12, the estimate of inoperability was based on interpretation of the patient's general condition, histologic misinterpretation, and failure to explore.   In Cases 14, 15, and 16, a second surgical exploration was not offered to the patient as a natural and logical consequence of the incorrect estimate of the gross pathology.   In Case 13, thoracic exploration was not done, not only because of the incorrect histologic diagnosis but also because of an assumption that roentgen-ray study had uncovered metastases from the rectal lesion.

III.   CANCER VISIBLE BUT UNDIAGNOSED

There are many careful surveys in recent literature on the differential diagnosis and management of chronic inflammatory processes and ulcerations of internal organs.   For example, in the age group of maximum incidence of gastric carcinoma, early exploration of nonhealing gastric ulcers is being advocated in order to detect more gastric cancers in their operable phases. However, the group of four cases as shown in table 3 presents chronic visible ulcerations where the establishment of the diagnosis was possible by biopsy. They are included to show that even those easily accessible lesions are at times not given the benefit of tissue examination.

The histories of the cases summarized in table 3 follow:

Case 17. This 69 year old female was admitted to Montefiore Hospital with a diagnosis of indolent varicose ulcer after having been under observation and treatment for eight years. She had first noticed a scratch on the right leg just above the ankle.

The scratch developed into an ulcer which slowly enlarged and steadily became worse. It resisted all forms of treatment, such as elevation of the foot, application of adhesive strapping, application of a plaster cast, and a wide variety of topical treatment. There was no objective or subjective improvement.   During the six months prior to admission the patient lost 35 pounds in weight and developed anorexia.

On admission to Montefiore Hospital in February, 1948, a deep ulcer was found, covering one-third of the leg laterally and extending a little medial and posteriorly, its edges somewhat raised and pearly (see figure 10).   There were enlarged glands in the right inguinofemoral region.   There were no varicosities of either of the lower extremities.   The skin of the extremities was shiny and atrophic.   There was mild anemia.   Shortly after admission specimens were taken from five different sites, four from the edges of the ulcer and one from its center.   Histologic examination revealed basal cell carcinoma in all five specimens.   An inguinal lymph node removed for biopsy showed only chronic lymphadenitis.

TABLE III

Cancer Visible But Undiagnosed

Case No.	On Admission	Final	Errors and Duration
17	Indolent varicose ulcer.	Basal cell carcinoma.	No biopsy; 8 years.
18	Ulcer of leg undiagnosed.	Basal cell carcinoma.	No biopsy; 4 years.
19	Indolent ulcer, chronic atrophic acrodermatitis.	Squamous cell carcinoma with extension to inguinal lymph nodes. Chronic atrophic acrodermatitis.	No biopsy; several months.
20	Varicose ulcer.	Squamous cell carcinoma. Chronic atrophic acrodermatitis.	No biopsy; 3 years.

On April 1, 1948, an extensive excision of the entire ulcer, including its fascial base was performed, followed by a split thickness skin graft completely covering the defect. Examination of the surgical specimen revealed a large thick piece of skin and subcutaneous fat, 17 by 12 cm. and varying from 1 to 2 cm. in thickness, with several pieces of fascia.   The edges of the ulcerated area were rough, abrupt, and pearly in character.   Microscopic examination showed ulcerated basal cell carcinoma with extension to the fascia.

The postoperative course was smooth.   The initial graft was estimated to have made approximately 90 per cent take.   The defects remaining at the edges were covered with pinch grafts at a later operation.   The patient is well, has no pain, and is ambulatory.   It is of interest that some years before this patient had radium therapy administered to a lesion over the left cheek.

In review of this case it is noted that, despite the very long history and despite the absence of visible varicosities in either extremity, this patient was treated on a presumptive diagnosis of varicose ulcer for eight years.

Case 18.   A 63 year old female reported that, following a mild trauma, a crusted lesion formed on the anterior surface of the right leg.   It was painless and there was rarely bleeding.   There were no varices and no signs of inflammation.   The lesion was treated with many medicaments for four years but never healed.   The lesion was small, about 1 cm. in diameter.   It was removed in toto with a good margin of sur-

FIG. 10. *Case 17.* Basal cell carcinoma of leg.

rounding skin. The histologic examination revealed basal cell carcinoma. There were two distinct lesions in the specimen.

Case 19. A 66 year old female was referred to our hospital in December, 1943, with a diagnosis of "acrodermatitis chronica atrophicans with severe ulcerations about the ankle with frequent profuse bleeding." Her skin ailment began some 38 years before with pain, swelling, and redness of the right hand. While this area gradually healed, new areas became affected until her entire body, with the exception of the head and neck, gradually became involved. Severe pruritus persisted, and ulcerations secondary to scratching and infection appeared. All these ulcers healed, leaving numerous scars. A few months prior to this patient's admission, one small ulcer appeared on the right ankle which resisted various forms of treatment, grew in size and depth, and shortly before admission bled profusely. She became weak and lost considerable weight.

On admission to Montefiore Hospital in November, 1946, examination revealed a pale, obese, chronically ill woman with marked atrophy of her entire skin except the head and neck, and several superficial scars. Severe deformities of several digits and toes were present. There was an enlarged gland, 3 cm. in diameter, in the right femoral lymph chain. Figure 11 illustrates the appearance of the ulcer on admission. As can be seen from this photograph, the entire medial aspect of the right ankle was the seat of a fungating, granulating mass which was necrotic, bled easily, and in places

was covered with a purulent foul-smelling exudate. This tumor extended into deeper tissues. It was fairly sharply demarcated from the surrounding skin by a raised grayish-white border. The remainder of the physical examination and laboratory data were noncontributory.

A biopsy taken from the tissue at the border of the mass revealed a verruca-like hyperplasia and hyperkeratosis with transformation to squamous cell carcinoma, and with evidence of chronic and acute inflammation. Aspiration of the enlarged femoral lymph node yielded tissue fragments interpreted as metastatic squamous cell carcinoma.

FIG. 11. *Case 19.* Squamous cell carcinoma in chronic atrophic acrodermatitis.

A mid-thigh amputation, followed by dissection of the ileofemoral lymph nodes, was performed. The patient's post operative course was uneventful; the stump healed by primary intention. Follow-up revealed no evidence of malignant spread.

From this patient's history and her findings on admission it is evident that she was suffering for at least several months from an extensive, growing and lately profusely bleeding ulcer. A diagnosis of cancer had not been made

because biopsy had not been taken. The spread of the disease, involving a femoral lymph node, was also unnoticed.

Chronic ulcerations are frequent complications of chronic atrophic acrodermatitis. Whenever such ulcers appear and fail to heal but continue to extend and bleed, one has to suspect strongly that malignant degeneration has taken place. The early beginnings of this malignant transformation are very difficult to diagnose. When in doubt as to their benignancy, a biopsy should be done. In view of the underlying severe atrophic skin disease, surgery rather than radiotherapy is the preferred treatment. Small lesions can be cured by simple excision, whereas in this instance, one leg had to be sacrificed and inguinofemoral lymph nodes dissected to achieve the desired results.

Case 20. A 60 year old female was referred to our hospital with the history that she had been suffering with varicose ulcers of both legs intermittently for the past 15 years. During one period—in 1939—these ulcers were healed. In the past three years the tissues of both legs had again broken down. It was thought that hospitalization to clear the ulcers was her only hope for a cure, as the areas involved were too extensive to expect healing without some form of skin grafting.

On admission the history was supplemented as follows: She had been suffering from varicose veins for the past 31 years. The ulcers had first appeared 16 years before; they would heal and then break down intermittently. Five years before admission, ulceration began around both ankles, becoming progressively worse during the last nine months. Twenty-nine years before, following pregnancy, the patient developed within a matter of days a generalized skin change. The skin became brownish, very thin, and wrinkled.

On admission to Montefiore Hospital in September, 1946, patient was described as obese. The only pertinent findings were confined to the skin, which showed a diffuse brownish pigmentation over the trunk and limbs; the skin was paper-thin, atrophic, and through the skin the dilated veins were visible. In some areas there was a mild degree of inflammation with telangiectatic vessels. The changes over the lower limbs are illustrated in figure 12. Numerous calcified plaques, up to 1 cm. in thickness and 6 cm. in greatest diameter, were seen and felt over both thighs. On the inner aspect of the left ankle, not seen in this photograph, there were a few scattered areas of serpiginous ulcers. The dorsalis pedis pulses were present. Pulsations of the posterior tibial artery were not examined because of ulcerations. The diagnosis made by the admitting physician was ulcerations secondary to varicose veins with superimposed inflammatory changes. Treatment included tyrothricin dressings and elevation of legs. Her condition improved with healing of the ulcers except for the one on the right ankle, which remained uninfluenced. A biopsy from the edge of the lesion was taken and a diagnosis of squamous cell carcinoma was made. There were a few suspicious lymph nodes palpated in the right inguinal area which were biopsied and found to represent chronic lymphadenitis only. A mid-thigh amputation was performed. A large irregular ulcer, 15 cm. in greatest diameter, was seen involving the dorsum of the right foot. The base of the ulcer was necrotic, hemorrhagic, granular, reddish, and contained an opaque grayish-white firm tumor. Its edges showed elevation and irregularity. The tumor extended into the subcutaneous tissue. The patient had an uneventful postoperative recovery. Up to the present time there has been no recurrence.

This case history shows considerable similarity to the one just described. As in the previous case, ulcerations accompanied a chronic skin disease.

Fig. 12. *Case 20.* Squamous cell carcinoma in chronic atrophic acrodermatitis.

These ulcerations healed slowly and recurred frequently. In the latter case, varicosities played an important rôle. According to the patient's history, ulcers over both ankles had persisted for several years. The lesions on admission, though interpreted as ulcers secondary to varicosities, were different in appearance from varicose ulcers. The dorsum of the right foot was the seat of a tumor which had existed for a long period of time before it reached its large dimensions. While the serpiginous ulcers on the left foot healed completely following conservative treatment, the "ulcers" on the right remained uninfluenced. It is easy to understand how the malignant nature of such an ulcer in a patient with extreme varicosities and a history of recurrent ulcers remained unrecognized. Here, as in the case history of the

previous patient, early biopsy of the superficial lesion would have saved the patient's leg, and a simple excision of the malignant ulcer may have sufficed.

All of these patients are alive. Three (Cases 17, 19, and 20) required a major surgical procedure; two (Cases 19 and 20), amputation. It is of interest to note that both of these patients developed cancer in skin already affected by chronic atrophic acrodermatitis. The relationship of these two diseases is still a subject for debate in the literature. Certainly it would appear that an ulceration of more than a few months' duration not clearly attributable to vascular inadequacy should be studied for malignant changes, especially if occurring in chronic atrophic dermatitis.

DISCUSSION

The cancer field during the last decade has been characterized by slow and steady progress. Biochemical data are being accumulated. Hereditary, viral, chemical, hormonal, and other factors which exert an influence on the development and growth of animal and human cancer are under close scrutiny. The technics of early cancer detection are being improved, and a campaign to educate the public to recognize early signs and symptoms of cancer is being waged. Surgical methods aimed at the extension of operability are being refined. Delay in seeking medical advice, attributable to patients' neglect, is being reduced.

This paper, however, deals with another aspect of the field of which but little is appreciated among the medical profession. It presents in the first two sections case histories of patients who were grouped as suffering from advanced cancer but were salvageable. No new diagnostic or therapeutic technic is described. Nevertheless, it is hoped that, by adopting a searching and critical approach in the acceptance of such cancer labels, progress may be made. Similarly, it is hoped that the case histories of the third group of patients will stress the importance of constant vigilance for the presence of cancer, though it may be entirely unsuspected.

The first group of patients was labeled "advanced terminal cancer." As pointed out in the case histories, none of these patients suffered from malignant disease. Let us now analyze the few patterns which appear and re-appear and are responsible for diagnostic errors.

In five of these patients, commonly used diagnostic procedures of proved value were omitted. For example, in Case 1, an obstructive lower bowel lesion was diagnosed without sigmoidoscopy and barium enema. A permanent colostomy was maintained for years; simple bimanual digital examination through the rectum and distal stoma would have proved the absence of obstruction and would have led to a more complete search for the cause of the symptoms. In Case 3, the prompt therapeutic response to liver extract of a patient with "secondary anemia" should have suggested the need for a more complete hematologic study, such as examination of bone

marrow.   In Case 5, the presence of a retroperitoneal mass should have suggested immediately the need for intravenous pyelography.

In five of these cases in Group I, an erroneous estimate of the nature of the gross pathology was made by the operating surgeon.   For example, in Case 4, an inflammatory lesion of the rectosigmoid was labelled "irresectable tumor."   This error was compounded by one which occurred in two other cases (1 and 2) in this group: failure to support a gross diagnosis by obtaining a biopsy specimen.   It is recognized that in some instances obtaining a biopsy is not practicable.   But in Case 2 it would seem that removal of a small nodule from the breast would have been mandatory before instituting radiation therapy.

Of all available diagnostic aids, histopathology is accepted as the most reliable.   But the results of histopathologic examination must be fitted into the clinical pattern and not accepted uncritically.   It is well known that in an occasional case histopathologic interpretation may fail.   Faulty interpretation was noted in Cases 6, 9, and 10.

Different diseases can produce similar roentgen-ray patterns.   Here again the entire clinical pattern should be decisive, rather than one diagnostic method alone.   In four cases (3, 7, 9, and 11), errors of interpretation occurred.   In Case 7, a patient with an intrathoracic mass had roentgen-ray evidence of bony abnormalities which were interpreted as metastatic. The mass was inflammatory and the osseous changes represented only osteoporosis.

It can be seen that in Group I the same errors occur several times in different patients, and that in some instances more than one error was made. The same is true of the cases falling into Group II.   In these cases the diagnosis of cancer was correct but the estimate of operability was not.   The course of these patients would have been altered had primary or secondary exploratory laparotomy been given consideration as a diagnostic aid.

In the five examples of Group II, the errors enumerated in discussing Group I are found to recur.   For example, an enlarged lymph node in proximity to a malignant lesion can well be inflammatory (see Case 15).   In another example (Case 13), a rectal polyp was judged as malignant by one pathologist and as benign by another; radiographic bone changes, observed in this same patient, were interpreted as metastatic by one radiologist and traumatic by another.   Moreover, it is realized that objective criteria of operability cannot be given.   Operability of a lesion depends not only on objective findings but also on the skill and experience of the operator.   It is gratifying to note, however, that fewer assumptions are being made and that a more inquisitive and radical approach is prevailing.

The third group of patients is characterized by one basic diagnostic omission: there was no attempt to secure the diagnosis by histopathologic examination.   The four patients of this group are selected because of the long duration of a visible lesion.   For instance, patient 20 had a huge

fungating tumor which was undiagnosed for three years.   The lesson which these cases teach us is the need for securing diagnosis prior to any therapy. Sometimes this represents a difficult task.   We believe it is preferable to perform an exploratory thoracotomy or laparotomy for diagnostic purposes than to delay detection of a case in a phase in which it is still amenable to treatment.   Biopsy of a superficial lesion is certainly one of the easiest procedures in medicine.

SUMMARY

Case histories of 20 patients are given in whom: (1) the diagnosis of terminal cancer was made and no cancer was present; (2) the diagnosis of terminal cancer was made although curable cancer was present; (3) the diagnosis of cancer was not made although a visible lesion was present for a long period of time.

The importance of complete clinical evaluation using all available diagnostic aids is stressed.   The danger of attaching the terminal cancer label to a patient on the basis of insufficient evidence is illustrated.   The point of view of taking nothing for granted is suggested.

CONGENITAL ABSENCE OF THE GALL BLADDER— A POSSIBLE HEREDITARY DEFECT *

By J. LESTER KOBACKER, M.D., F.A.C.P., *Toledo, Ohio*

CONGENITAL absence of the gall bladder can be considered a medical rarity, and its observed occurrence has not been sufficient to establish clearly the factors underlying its development nor to determine means of identifying it prior to operation or necropsy. The admirable review of Dixon and Lichtman [1] established the known reported cases of the condition as numbering 60 from 1900 to 1945. In 1947 Latimer, Mendez and Hage [2] searched out additional cases and added three of their own, bringing the total number to 71. Not all of these presented every criterion of clearly absent gall bladder, yet it may be said that most of the cases were reasonably satisfactory representatives of this strange anomaly. Many earlier writers have pointed out the fact that certain species are found to possess no gall bladder (nine species of birds, 17 species of fish, some rodents, and the deer, camel, horse, rhinoceros and elephant), [3,4,5,6] and almost all articles on the subject have discussed the embryology of the organ and its related structures. Many theories regarding the origin of the anomaly have been advanced, such as fetal peritonitis, syphilis, maternal toxins, etc., but most writers have favored as the sole factor involved the chance embryologic failure of the anlage to develop. No mention has appeared regarding the possibility that heredity, rather than chance, determines the appearance of the anomaly.

It has been recognized and emphasized that evidences of biliary disease characterize many, if not all, such cases encountered in the living patient. The report of Finney and Owen, [7] reviewing 46 cases, pointed out that in 11 completely reported cases, calculi in the common duct occurred in all. Ten of the 11 had dilated ducts. Gaseous indigestion, intolerance of fats, pain, and occasional jaundice were cited as clinical manifestations. In the report of Dixon and Lichtman, [1] 24 of 34 which were found at operation had been operated on for suspected cholecystic disease. Jaundice appeared in 48 per cent and stones in 27 per cent of the patients over 45; 73 per cent had symptoms. The authors infer that long continued absence of a gall bladder predisposes to symptoms.

Since one of the chief diagnostic tests for serious gall bladder disease, namely, the failure of visualization by cholecystography, will also be positive in these cases of absence of the gall bladder the clinical diagnosis of the latter condition is obviously difficult. It has been said that no case of congenital absence has been properly diagnosed before operation (or autopsy). If the following report indicates a newer concept of etiology, the possibility of preoperative suspicion may be enhanced.

The congenital anomalies which are hereditary are numerous indeed, and the textbooks on heredity are filled with examples ranging from polydactylism and albinism to geographic tongue.   That congenital agenesis of the gall bladder might belong to this long list is not beyond reason, and the following sequence would seem to point to this possibility.

CASE REPORTS

Case 1.   A 43 year old female was seen September 8, 1939, with the complaint of progressive arthritis of five years' duration.

Family History: Had been married 23 years and had two children living.   There had been no miscarriages.

Past History: The tubes had been ligated and appendectomy performed 19 years ago, tonsillectomy 12 years ago.   At about the same time, all upper and several lower teeth were extracted.   Measles six years ago.

Habits: Not unusual.

Menstrual: Menopause had begun.

Present Illness: In addition to symptoms and signs of arthritis—pain, swelling, distortion of joints—the patient had noted flatulence, epigastric pressure, and great weakness.

Physical Examination: The following positive or pertinent findings were noted: (1) Some evidence of dental infection in remaining lower teeth.   (2) Tenderness in the right upper quadrant.   There was a midline lower abdominal scar.   (3) The small joints of both hands and feet displayed limitation of motion, fusiform enlargement with tenderness, and some atrophy of the carpal interossei.

Laboratory Findings: Urine: entirely negative.   Hemoglobin, 79 per cent; white blood count, 6,400.   Differential count: Polynuclears, 65 per cent; lymphocytes, 31 per cent; monocytes, 1 per cent; eosinophiles, 2 per cent; basophiles 1 per cent. Blood Kline: negative.   Sedimentation rate (Cutler): 16.5 mm. in 60 minutes.   Basal metabolic rate—minus 19 per cent.   The cholecystogram by the oral method, on two occasions, showed no visualization.

Operation was performed on October 12, 1939, by Dr. Wade Stone (since deceased).   The abdomen was opened through a Kocher incision.   The common duct was readily identified.   No gall bladder was found, although the common duct was opened and probes inserted into right and left hepatic ducts and down into the duodenum.   The round ligament was severed to make a thorough search possible, but no gall bladder could be found.   Three large glands were noted along the common duct and two were removed, one for section and one for culture.   There were adhesions between the liver and the diaphragm.   The pancreas appeared normal.

Exploration of the lower abdomen showed the appendix to have been removed. The uterus was present.   Numerous omental adhesions were encountered.

A **T** tube was placed in the common bile duct, which was not dilated.   The wound was closed routinely.

Pathologic report of a section of the removed lymph gland was reported as showing "slight to moderate chronic infectious lymphadenitis."   Cultures were sterile.

On October 24, 1939, brominol was injected into the drainage tube and the report was: "Studies of the liver radicles and biliary ducts show the brominol which also passes readily into the small bowel.   There is no evidence of gall bladder or cystic duct seen."

The possibility of a surgical extirpation 19 years earlier was carefully considered but it seemed improbable, not only because the patient had no knowledge of any such maneuver and had suffered no hepatic or biliary symptoms previously, but also because

it would have been very difficult indeed to have removed a gall bladder through the midline lower abdominal incision.

Case 2. About a year later the above patient's sister consulted me because of gastric disturbance of long duration. She was seen first on December 21, 1940, with a complaint of "gas and belching" for 14 years.

Briefly, her essential anamnestic material was as follows: (1) There had been jaundice at 18. She had always had some stomach trouble since. (2) Scarlatina at 12, and mastoidectomy at 16. (3) She had noted periods of flatulence, anorexia and eructations for many years. At all times there was a sensation of pressure in the epigastrium. Distinct from these, she had occasional spells of pain across the lower abdomen, especially on the right.

The pertinent physical findings were localized to the abdomen. There was slight tenderness over McBurney's point. More marked tenderness was noted under the right costal margin.

Laboratory data, including blood counts, urinalysis, and blood Kline, were negative except for a slight hyprochromic anemia.

Cholecystographic studies after both oral and intravenous administration of the dye failed to show a gall bladder shadow.

During the ensuing year on bile salts and dietary control her biliary symptoms subsided, but she had several brief attacks of lower abdominal pain. Since she lived some 30 miles from the city, she was never seen in one of these. Notation was made of the possibility of recurrent appendicitis and of the *possibility* of another instance of agenesis of the gall bladder.

Upon leaving for military service in 1942, the author explained the situation to the patient with the request that she relay such information, should it ever be necessary to operate on her abdomen.

In August, 1946, the patient returned to state that about two years previously she had been operated on in another community. Absence of the gall bladder had been noted and the appendix removed.

Through the courtesy of Dr. F. L. Moore, of Fremont, Ohio, I obtained the hospital report, including the operative note. These are appended:

Provisional Diagnosis: Chronic gall bladder disease.

Final Diagnosis: Congenital absence of the gall bladder.

Case History: For several years patient had been having spells of gas on stomach and pains in the right upper quadrant.

Present Illness: Tenderness in the gall bladder area. Frequent extrasystoles.

Operative Note: Preoperative diagnosis: Chronic gall bladder disease. *Postoperative diagnosis:* Subacute appendicitis.

Findings: Congenital absence of the gall bladder. Common duct was dissected out and no calculi were present. Appendix was large and showed active inflammation.

Operation: Right paramedian incision. Appendix removed and stump inverted. Incision closed.

In a verbal communication, Dr. Moore informed me that a very careful inspection was carried out and nothing was noted to suggest either an aberrant or an atrophic gall bladder.

Thus far there were two sisters in whom definite agenesis of the gall bladder was established. The absence of gall bladders in the two sisters stimulated a study of other members of this family. There were six other sisters, five of whom were available for investigation.

TABLE 1

1.	Mrs. H. A.	Age 52	Nonvisualization
2.	Mrs. V. G.	Age 52	Normal visualization
3.	Mrs. W.	Age 48	Normal visualization
4.	Mrs. M. M.	Age 45	Nonvisualization
5.	Mrs. M. H.	Age 56	Nonvisualization

Table 1 presents the cholecystographic findings. Two other members of the family were available for roentgenographic examination. These were daughters of No. 5 in table 1 and of the second operated case, respectively, both of whom had mild dyspeptic symptoms. Each was 18 years old and in each there was nonvisualization by the cholecystogram. Thus, three of five examined siblings of the two proved cases had possible agenesis, and two next generation individuals presented presumptive evidence of gall bladder absence. The latter two were immediate descendants of cases revealing absence of the gall bladder. Figure 1 presents the relationships in the family graphically.
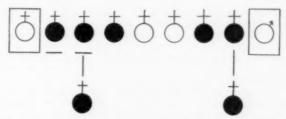

Fig. 1. Family graph. Shaded cases showed non-visualization of the gall bladder. Underlined cases were operated upon. Cases encased were not available for study.

Thus far, the author has found no suggestion in the literature that the anomaly of agenesis may be hereditary and that several members of a family may be affected. Latimer et al.[2] stated: "For evident reasons, a preoperative diagnosis of congenital absence of the gall bladder is extremely difficult if not impossible . . . there being no reported case of the diagnosis made before operation or postmortem examination." In the presence of a family picture such as is presented here, this probability must be considered. It was permissible in one case here reported to anticipate the possible discovery of the agenesis before operation, and other investigations of families may establish the familial hereditary bases of this anomaly and may occasionally permit a preoperative diagnosis in such groups.

The histories of the proved cases here bears out the experience of other authors, that gall bladder absence is accompanied by dyspepsia and symptoms of biliary disturbance, and the findings suggest that inflammatory and structural changes underly these manifestations.

Summary

The cases of two sisters presenting agenesis of the gall bladder are reported.   Both were explored surgically and in one case choledochography was performed.   Three of five sisters of the reported cases showed failure of visualization on cholecystography.   Gall bladder in two second generation girls also failed to visualize.   All the abnormal cases had mild to moderate dyspeptic complaints, thus confirming previous experience with cases of agenesis of the gall bladder.

No previous intrafamilial occurrence of this anomaly has been reported. In view of the striking incidence inferred in the reported family, there is evident need for attention to the possibility that absence of the gall bladder is an hereditary anomaly.   It is felt that a non-visualization of the gall bladder merits especial notice in any family in which a congenital absence already has been established.

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CASE REPORTS

ACUTE COR PULMONALE *

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Pulmonary infarction is a relatively common condition, but acute cor pulmonale is seldom diagnosed. This may be due to the transient nature of the process, or to confusion with other disease states. The purpose of this report is to present an interesting case of acute cor pulmonale and to draw attention to the confusion in the diagnosis of this condition.[1]

Case Report

A 22 year old white bricklayer was admitted with chief complaint of severe sharp pain in the left lumbar region of one day's duration. His past history included a duodenal ulcer while in military service in April, 1945. In 1944 he had received a superficial gunshot wound of the left thigh. The family history was noncontributory.

On October 5, 1946, he developed a "head cold" associated with mild cough productive of occasionally blood-tinged sputum. He felt well until October 13 when, while seated in the theatre, he suddenly developed a severe, sharp, non-radiating pain in the left lumbar region. He had no genito-urinary or gastrointestinal complaints. Walking made the pain worse. The pain continued, and later was present in the left hip.

The next day, October 14, he was admitted to the Reception Service. Examination revealed a temperature of 101° F. The heart and lungs were normal. The abdomen was rigid, without localized tenderness or rebound, and no masses were palpable. There was marked tenderness in the left costovertebral angle. On the morning of October 15, the pain radiated across the abdomen to the lower right chest, then to the upper right chest. The pain was sharp and aggravated by inspiration, and it made respiration difficult. Cough became more severe and on two occasions was productive of a large clot of blood.

Examination on October 15 revealed a temperature of 100.4° F.; pulse rate was 84; respirations 32; blood pressure 130/70 mm. Hg. The patient was acutely ill, in severe distress, bent over in pain, and coughing up blood-tinged sputum. The eyes, nose and throat were normal. The heart was not enlarged clinically and the sounds were of good quality, without thrills or murmurs. Rhythm was regular sinus. Chest expansion was diminished bilaterally, with depressed breath sounds at both bases, absent breath sounds in the right axilla. No râles or friction rub were noted. The abdomen was spastic throughout, with some tenderness but no masses. There was severe bilateral costovertebral angle tenderness, greater on the left than on the right. The extremities were normal. Rectal examination was normal.

Laboratory data on admission were as follows: Hemoglobin 14.9 gm. per cent; white blood cells, 12,800, with polymorphonuclears 79 per cent, lymphocytes 19 per

cent, monocytes 2 per cent; erythrocyte sedimentation rate was 20 mm. Wassermann and Kahn tests were negative. Sputum culture showed hemolytic streptococcus. Urinalysis was normal. Roentgen-ray studies on October 14 showed clear lung fields with normal diaphragms and clear costophrenic sulci; the cardiac contour was normal. No free air was seen in the peritoneal cavity. On October 15, roentgen-ray revealed slight haziness of the outline of the outer half of the right diaphragm, with a questionable small pneumonic infiltrate at the right base. Electrocardiogram showed right axis deviation with a deep S₁.

It was felt that the patient was suffering from an acute pneumonitis. Penicillin therapy was started: 50,000 units were given every three hours. The patient remained acutely ill, with temperature ranging between 101 and 102° F. The sputum was blood-tinged. There was marked tachypnea. Abdominal tenderness and spasticity persisted. Breath sounds were diminished in the right axilla, and a pleural friction rub was heard in the right third intercostal space. On October 16, roentgen-ray revealed a small area of pneumonitis at the right base. The sputum remained blood-tinged. On October 18 the patient began to feel better. His abdomen became less tender and spastic. There were slight dullness and diminished breath sounds in the right axilla. Penicillin was continued. On October 20 he became afebrile.

On October 23 the patient became acutely ill, with severe generalized abdominal pain, mainly in the right upper quadrant, radiating to the right shoulder. His abdomen again became spastic, with tenderness in the right upper quadrant. The sputum was frankly bloody. There was an equivocal Homan's sign on the left. White blood cells were 17,350, with 90 per cent polymorphonuclears. It was felt that the patient was suffering from multiple pulmonary infarcts, with the left leg as a possible source. A left common femoral vein ligation was performed. A free flow of blood was obtained both above and below the site of ligation.

The next day his temperature rose to 103.6° F.; the patient was acutely ill, cyanotic, and coughing up frankly bloody sputum. He complained of constant discomfort in the left upper chest anteriorly. Examination revealed a pulsation and systolic thrill in the second left interspace, adjacent to the sternum. The sounds were very loud and overactive, and there was a loud harsh systolic murmur in the second left intercostal space over the site of the pulsation, with P₂ accentuated. Roentgen-ray revealed a pleural effusion at the right base, with fluid extending to the fifth intercostal space in the anterior axillary line. A blood culture with penicillinase was negative. The dose of penicillin was increased to 100,000 units every three hours. An electrocardiogram revealed no change from the one taken on admission. High fever continued, with cyanosis and bloody sputum.

On October 26 the patient appeared better. The abdomen was less spastic. There was dullness at the right base, with diminished breath sounds and whispered voice. The pulsation and murmur persisted over the second left intercostal space. Blood pressure was 110/65. Roentgen-ray revealed effusion and parenchymal involvement of the lower third of the right lung. On October 28 the left calf became swollen and tender. Blood culture was again negative. On October 29 the temperature was still high and there was pain in the right groin. Pulmonary findings were dullness at the right base posteriorly and in the axilla, with bronchial breath sounds and bronchophony. The pulsation and murmur persisted in the second left intercostal space, but a thrill was no longer palpable. Venous pressure was 130 mm. of water; arm-to-lung time (paraldehyde) was eight seconds; arm-to-tongue time (calcium gluconate) was 18 seconds. Dicumarol therapy was begun.

On October 30 the cough was less productive but the sputum continued blood-tinged. Pulmonary and cardiac findings were unchanged. His left leg was swollen, red and tender, and a cord-like structure could be felt on the medial aspect of the left thigh. The medial aspect of both thighs was tender. It was felt that there was

a spread of the thrombosis above the ligation site to the contralateral leg, and that the reaction in the left leg was greater than could be caused by ligation.

Penicillin and Dicumarol therapy were continued. The pulsation and murmur in the second left intercostal space and the accentuated P₂ still were present. The temperature spiked to about 102° F. daily. The sputum continued to be blood-tinged. The left leg became edematous and less painful; the right leg was more painful, and gradually became edematous. Signs over the right lower chest became less pronounced, and roentgen-rays revealed absorption of the effusion at the right base, and gradual resolution of the pulmonary infiltrate. Penicillin was discontinued on November 9 because of the absence of apparent effect. At the same time the temperature fell and became normal on November 11. It remained normal thereafter.

The pulsation disappeared from the second intercostal space; the murmur became less and less audible; P₂ was no longer accentuated. The sputum continued bloodtinged until November 21. Dicumarol was stopped on November 23. There was slight bilateral pretibial edema, but no pain. The chest was clear on November 24. Roentgen-ray showed blunting of the right costophrenic sinus and flattening of the right diaphragmatic leaflet. The heart and aorta were normal. There was accentuation of the markings at the base of the right lung. Electrocardiogram showed no significant change from earlier tracings. White cell count was normal. The patient was discharged from the hospital on December 6, 1946.

The patient returned for follow-up examination in September, 1947. He was asymptomatic except for some edema of the feet on standing. He had passed several stringent physical examinations, which included severe physical tests. Examination of the chest was normal. The heart was not enlarged; there were no murmurs, thrills or abnormal pulsations. No pulsation thrill or murmur was elicited in the second left intercostal space. Blood pressure was 120/78. The abdomen was normal. There were slight pretibial edema and a few superficial varicosities bilaterally. Electrocardiogram was similar to those taken during hospitalization. Roentgen-ray and fluoroscopic examinations revealed clear lung fields and normal heart and aorta.

DISCUSSION

The syndrome of acute cor pulmonale first was described by White[2] and McGinn and White[3] in 1935. According to their description, the syndrome consisted of an increased prominence and pulsation in the region of the second and third intercostal spaces just to the left of the sternum, which area overlies a dilated and sometimes overactive pulmonary artery and conus. There may be a loud systolic murmur and an accentuated pulmonic second sound if the circulation is not too much obstructed. A friction rub and gallop rhythm may be noted. There are frequently dilatation and increased pulsation of the jugular veins, and cyanosis. These symptoms usually have an abrupt onset, with dyspnea and thoracic oppression. Right heart failure may be a part of the syndrome. Occasionally shock is present and may be so severe as to obscure the entire picture of acute cor pulmonale.

This syndrome is seen following massive pulmonary embolism secondary to phlebothrombosis. The electrocardiogram in many cases reveals a lowering, flatness, or inversion of T_2, inverted T_3, a wide or deep S_1, inversion of QRS_3, and an inverted T in CF_4. The entire syndrome may subside rapidly or persist for a few days. Since it is associated with pulmonary embolism, fever and leukocytosis are usually present.

In the case reported here, phlebothrombosis developed in a normal, healthy white male. His initial symptoms resulted from an acute pulmonary embolism. He improved at first but then became more severely ill, apparently following fur-

ther pulmonary embolization. The next day signs of acute cor pulmonale appeared, and these persisted for almost three weeks. Penicillin throughout this period had no apparent effect upon the course of the temperature. At approximately the same time that penicillin was discontinued, the temperature returned to normal. The electrocardiographic changes noted were consistent with those described above but did not include all the changes usually noted, and there were no serial changes. In all other aspects, this case follows the syndrome described by White[2] and McGinn and White.[3]

Myers[1] reported a case of gonococcal endocarditis of the pulmonary valve successfully treated with penicillin. His patient entered with signs of acute pelvic inflammatory disease due to the gonococcus, and probably infectious hepatitis. Eleven days after admission, the patient developed moderately severe pleural pain on the right side of the chest. A prominent systolic murmur was heard to the left of the sternum in the second interspace. There was a systolic thrill in the same area. Roentgen-ray revealed a diffuse infiltrate of the lower half of the right lung. Numerous blood cultures were negative, although gramnegative diplococci were cultured from the pleural fluid. The patient received large doses of penicillin. Her temperature returned to normal within nine days. Within three weeks the thrill at the base of the heart had disappeared and the systolic murmur was softer and less pronounced. Follow-up study revealed a soft, blowing, nontransmitted murmur in the second interspace to the left of the sternum. The course in this patient was compatible with that seen in acute cor pulmonale. In view of the rapid onset of the murmur and thrill, associated with severe right pleural pain and the almost complete clearing of physical findings, the diagnosis of acute cor pulmonale seems more probable than that of acute bacterial endocarditis.

SUMMARY

A case of acute cor pulmonale has been described in a previously healthy young white male, following pulmonary embolization secondary to phlebothrombosis of the legs.

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PSORIATIC ARTHRITIS *

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THE occasional coexistence of rheumatoid arthritis and psoriasis has been acknowledged by clinicians for many years. The question of the causal relation-

ship of one disease to the other has been the subject of numerous papers. The question has also been raised in recent years as to whether psoriasis may ever be responsible for a joint disease which is not rheumatoid arthritis. The present report deals with the latter question.

HISTORICAL ABSTRACT

According to Dawson,[1] attention was first called to the presence of joint pains in patients with psoriasis as early as 1822. Comroe[5] states that this association was further studied by Bourdillon in 1888.[2] In discussing a paper by Hench,[3] O'Leary reported eight cases of arthritis among 1,400 patients with psoriasis. Dawson and Tyson[4] found 26 cases of psoriasis in 1,000 patients with rheumatoid arthritis and only three cases of psoriasis in an even larger group of cases of osteoarthritis. Comroe[5] states that psoriasis may be found in from 1 to 3 per cent of patients with rheumatoid arthritis and, further, that this arthritis is usually indistinguishable from the usual form of rheumatoid arthritis on both clinical and roentgenologic grounds.

A roentgen survey by Popp and Addington[6] of the hands of 24 patients with psoriatic nail changes revealed no bone changes but only periarticular swelling. Hench[3] reported a case with psoriasis for 18 years, ankle joint arthritis for six years, and recent arthritis of the terminal joints of some fingers. Here roentgenray revealed some destructive and atrophic arthritis of the tarsal joints only. Jeghers and Robinson[7] reported a similar case with chronic psoriasis and widespread joint involvement. The roentgen-ray revealed periarticular swelling and slight destructive and atrophic changes of bone which were interpreted as con-

FIG. 1. Note psoriatic nail changes and normal terminal joints of left middle and right index finger.

FIG. 2. Ability to make tight, painless fists. This is rarely possible when rheumatoid changes are present in hands.

FIG. 3. Right hand, showing normal terminal interphalangeal joint of index finger and destructive lesion with flexion of corresponding joint of third, fourth and fifth fingers.

sistent with rheumatoid arthritis. In both the above cases, improvement in the psoriasis under treatment was paralleled by improvement in the arthritis.

Hench [8] pointed out that when the hands or feet are involved there is a tendency for participation of the terminal joints, especially in those digits which also exhibited nail changes. Photographs were published of such a case.

Cases have been reported in which there was such marked atrophy and destruction in the bones of the hands and feet that the phalanges had almost completely disappeared,[9, 11] however, Comroe remarks that such extensive bone and joint changes with loss of bone in the hands and feet have been described in patients without psoriasis.

Fig. 4. Left hand with uninvolved terminal joint of middle finger and involvement of second, fourth and fifth terminal joints.

Epstein [10] stated that there were about 200 cases of psoriatic arthritis reported in the available literature to 1939. In scanning this group, as well as his own cases and those of colleagues, he was able to accept only 33 as definite cases in which the psoriasis had occurred before the arthritis, was chronic in nature, and in which there was a reasonable amount of synchronous activity between the psoriasis and the arthritis. He defined the arthritis as atrophic in type.

It is apparent that many authors have felt justified in using the term in patients who show a close relationship between the exacerbations of the psoriasis and the appearance or aggravation of joint lesions. Bauer, Bennett, and Zeller [11] reported the autopsy examination in one case of psoriatic arthritis where the histopathology did not resemble that of rheumatoid arthritis and suggested that the two diseases were possibly not the same.

CASE REPORT

The patient was a 58 year old peddler who was admitted to the Salt Lake City Veterans Hospital because of chest pain for six months. For 14 years he had had typical ulcer symptoms and for the past three months these had become worse.

The past history was of particular interest, since he had had "inflammatory rheumatism" at the age of 11, with painful, swollen, red joints of all the extremities, and was treated with bed rest for 90 days. He had never been told that there was a heart murmur.

For 25 years he had had skin lesions involving the knees, shins, elbows, scalp, and trunk, with summer improvement and winter exacerbation. He had noted that strict adherence to the ulcer diet, with large amounts of milk and cream, caused exacerbation of the lesions.

For 15 years there had been involvement of the fingernails to the extent that when they became thickened and deadened, he could whittle them off almost down to the base of the nails. At the time of onset of these nail changes he noted pain in the tips of both the fingers and toes, and six months later the terminal phalanges of most of the fingers became flexed. The involved joints were always more painful when the

Fig. 5. Psoriatic skin lesions and minimal toenail changes without deformity.
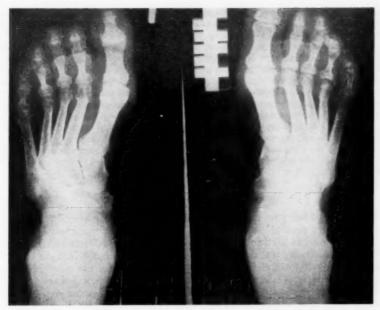
Fig. 6. Roentgen-rays of feet, interpreted as normal by radiologist.

dermatitis became worse. There was no history of any other joint involvement of any sort after the age of 11.

Physical Examination: Temperature, 98.6° F.; pulse, 75; respirations 20; blood pressure, 140/74. Patient was alert, well developed, well nourished, coöperative, and in no acute distress. Lungs were normal. The heart showed only frequent extra-systoles. Abdomen was normal. Prostate was enlarged 2 plus. The skin showed red, scaling, circinate lesions over the knees, both legs anteriorly and posteriorly, both thighs posteriorly, buttocks, scrotum, pubic region, elbows, thorax, and scalp (figure 5). The nails were thickened and contained dead white areas and many minute pits. These changes were less on the toe nails than on the finger nails, and were almost completely lacking in the nails of the left middle and right index fingers (figure 1).

The fingers, with the exception of the left middle and right index, all showed sharp flexion at the terminal interphalangeal joints (figure 1). There was slight thickening and tenderness of these joints, and they could not be extended. The changes were so striking that the patient was at first asked if he had formerly been a professional baseball player, which he denied. The remaining joints of the hands were normal, he could make good fists, and grips were quite normal (figure 2). The other peripheral joints of the extremities and the spine were entirely normal. There was no deformity of the toes (figure 5).

Laboratory Data: Hemoglobin 16.5 gm., white blood cells 10,000, polynuclears 29, lymphocytes 61, mononuclears 5, eosinophils 1, basophils 4, sedimentation rate 5 mm./hr.; serologic test for syphilis negative. Urine and stools normal. Blood uric acid 2.7 mg. per cent. Electrocardiogram revealed slight delay in activation of

the right ventricle. Biopsy of the skin lesion showed chronic, nonspecific dermatitis with slight parakeratosis and hypertrophy of the rete. Dermatologic consultant regarded the lesions as typical of chronic psoriasis.

Roentgen-rays of the lumbar spine, sacroiliac joints, and both feet were normal (figure 6). Roentgen-rays of the right and left hands revealed extensive changes in the distal interphalangeal joints of all fingers except the middle finger on the left and index finger on the right. The articular cartilages had disappeared and the cortices were irregular, with sclerotic as well as punched out cystic changes at the articular margins. There were no significant hypertrophic changes. The remaining joints of the hands and wrists were normal (figures 3 and 4).

Course: Roentgen-rays revealed a characteristic deformity of the duodenal bulb, and gastric analysis revealed 76° free and 87° total acid after histamine. On standard ulcer therapy the chest and gastric symptoms subsided. No attempt was made to treat either the psoriasis or the arthritis, since the patient had learned to live with his disease with surprisingly little difficulty.

COMMENT

This case is being reported because of its bearing on the question of the existence of pure psoriatic arthritis as an entity. Many of the cases seen on a chronic rheumatism ward and many of those reported in the literature are cases of advanced rheumatoid arthritis in which psoriasis also exists. In some of these cases, the skin and nail changes are typical of psoriasis and are not infrequently associated with changes in the terminal interphalangeal joints which are definitely not those seen in rheumatoid arthritis, i.e., the complete destruction of the articulating surfaces without ankylosis, resulting in flail joints. In patients with this combination, the larger joints of the extremities or spine are usually indistinguishable clinically from those of patients who have only rheumatoid arthritis without any skin complication.

This case presents several features which merit its being included with the small group of so-called "pure" cases of psoriatic arthritis in the restricted sense, i.e., without rheumatoid changes. The skin lesions preceded the joint lesions by many years. The joints involved became more painful during exacerbations of the psoriasis. The joints involved were terminal interphalangeal joints and none other.

Several additional features deserve emphasis: the flexion deformities of the distal phalanges as seen in this patient are distinctly uncommon in ordinary rheumatoid arthritis, and when they do occur there is practically always involvement of other joints of the hands; there was no evidence whatsoever of any type of abnormality in joints other than the ones described; the only terminal interphalangeal joints involved were those in which the corresponding finger nails showed definite psoriatic changes—one finger on each hand escaped both joint and significant nail involvement.

It is obvious that this patient has been fortunate in having a very slow and indolent process at work. Although the toenails showed slight psoriatic changes, there was no demonstrable joint involvement of the corresponding digits. It seems likely that if the pathologic process had been more dynamic there would have been involvement of more joints, as well as further destruction in the damaged joints. Whether progression to the condition of actual joint dissolution could occur in a patient such as this is a matter of conjecture, but it may be that

the coexistence of true rheumatoid arthritis is necessary before such extreme destruction occurs.

SUMMARY

A case is reported of "pure" psoriatic arthritis wherein the psoriasis antedated the joint changes by many years, the skin and joint lesions showed synchronous remissions and exacerbations, the joint changes were limited solely to the terminal interphalangeal joints of those fingers which also showed more than slight psoriasis of the nails, and there was no clinical or roentgen-ray evidence of change in any joint of the body other than the terminal joints of the fingers.

Although biopsy was not permitted, the available evidence in this case suggests that there is such a rare entity as arthritis specifically due to psoriasis.

The radiologic aspects of psoriatic arthritis will be discussed separately by another writer in a review based on this same case to be published in a radiologic journal.

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ENDOCARDIAL TUBERCULOSIS *

By EDGAR BARON, M.D., *Kecoughtan, Virginia,* and DALE W. RITTER, M.D., *Sherman Oaks, California*

INVOLVEMENT of the endocardium is one of the infrequent manifestations of tuberculosis and is usually associated with generalized miliary spread. Tuberculoma is even less common than either miliary tuberculous endocarditis or tuberculous extension from the pericardium or surrounding structure.

Baker,[1] who wrote an excellent review of the subject in 1935, presented five cases of miliary tuberculous endocarditis and one with a tuberculoma of the right atrium associated with tuberculous pericarditis. Mark[2] presented a case of tuberculous endocarditis of the pulmonary valve and referred to two other cases which were reported by Davie.[6] Ward[3] described a case of miliary endocardial tuberculosis with far advanced pulmonary disease. Bevans and Wilkins[4] reported a case of tuberculous endocarditis superimposed upon a congenital defect of the aortic valve with concomitant involvement of the mitral valve. Egidio[8] reported a case of tuberculosis of the aortic valve. About 200 cases appeared in the literature, according to Rosenbaum and Linn[5] and Rauchweiger and Rogers.[7]

CASE REPORT

A 53 year old Negro male was admitted to the Veterans Administration Hospital, Kecoughtan, Virginia on November 25, 1947. Two weeks prior to admission his left arm and leg had suddenly begun to shake for several minutes. This was followed
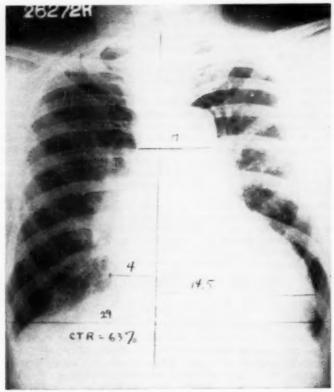
FIG. 1. Roentgenogram of chest, 1943, showing accentuated vascular markings in the right hilar region. The heart is enlarged to the left.
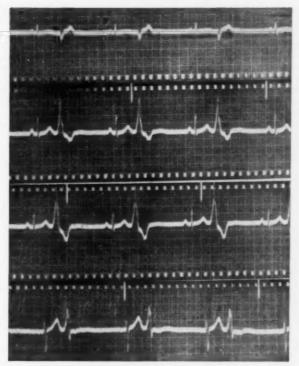
Fɪɢ. 2. Electrocardiogram, 1943, showing bigeminy with premature ventricular contractions.

by persistent weakness, more marked in the left leg. He had remained in bed until the day of admission, when he had had a similar episode.

He had previously been a patient in this hospital from June 8 to August 17, 1943. During the preceding five years, he had been treated by his private physician for six recurrent episodes of dyspnea, ankle edema, and cough. The episodes lasted several months and were associated with abdominal fullness and urinary frequency. He denied chest pain, hemoptysis, and orthopnea, but was aware of the existence of hypertension.

The family history was irrelevant. The past history included chickenpox as a child, gonorrhea in 1916, and influenza in 1918.

Examination at that time revealed him to be afebrile. The blood pressure was 190/110 mm. Hg. There were a few fine, moist râles at both lung bases. The heart was enlarged slightly to the left by percussion, and the point of maximum impulse was located in the fifth left interspace just outside the midclavicular line. Slight, bilateral, pitting ankle edema was present.

Laboratory studies revealed negative Wassermann and Kahn reactions. Urinalysis was negative. The hemoglobin was 12.4 gm., the erythrocyte count 4.12 million, and the leukocyte count 9,200. Roentgenogram of the chest (figure 1) was reported as showing accentuated vascular markings in the right hilar region. The heart was enlarged, with marked prominence of the left cardiac contour. There was calcium

deposition in the arch of the aorta. Electrocardiogram (figure 2) showed bigeminy, with premature ventricular contractions.

With bed rest and digitalis, his cardiac failure improved and he was discharged to the care of his private physician.

He was not seen again until November 25, 1947 when he was readmitted for the treatment of a left hemiparesis; this had developed about two weeks prior to entry. He described left sided clonic convulsions, followed by weakness of the left side of face, arm, and leg. Similar convulsions recurred on the day of admission.

Physical examination revealed a fairly well developed, well nourished Negro male, lying quietly in bed. The temperature was 98.2° F., the pulse rate 98, the respiratory rate 28, and the blood pressure 115/85 mm. Hg. The facial muscles were weak on the left. The lungs were clear to percussion and auscultation. The heart was moderately enlarged to the left by percussion, and the point of maximum impulse was diffuse and was centered in the sixth left intercostal space in the anterior axillary line.
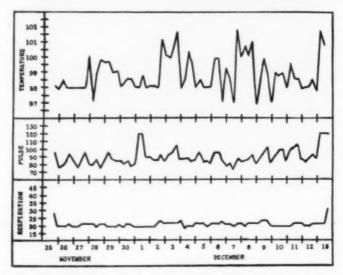
FIG. 3. Chart of temperature, pulse and respiration during last admission in 1947.

There was a soft apical systolic murmur, and a low blowing diastolic murmur was heard, best at the level of the fourth intercostal space to the left of the midline. The rate was regular and no thrills were present. There was a generalized mild abdominal tenderness but no rigidity. The liver and spleen could not be palpated. There was moderate weakness of the left arm and almost complete paralysis of the left leg. Deep reflexes were diminished in these extremities. The Babinski sign was questionably positive on the left.

Examination of the urine showed it to be acid, with a specific gravity of 1.011; test for sugar was negative; albumin was 2 plus; microscopic examination revealed 14 to 16 white blood cells, with occasional clumps, and many granular casts per high power field. The hemoglobin was 13.0 gm.; erythrocyte count 4.16 million, and leukocyte count 6,700, with 72 per cent neutrophiles and 28 per cent lymphocytes. The blood Wassermann and Kahn reactions were negative.

His course in the hospital was gradually downward. He remained weak, and was unable to get out of bed. On the seventh day after entry, he had a series of clonic contractions of the left side of the face, arm, and leg over a period of one and one-half hours. These were finally controlled by a total of six grains of sodium luminal and four drams of paraldehyde. On two subsequent occasions, several days later, he was noted to have twitchings of the left side of the face and tremors of the left arm and leg. Other than pain in his lower abdomen and left thigh on the thirteenth day, he had few complaints. He remained quiet following the administration of a narcotic. On the following day, he became confused, had to be fed by an attendant,

FIG. 4. Left auricular appendage, showing the adherent tuberculoma with super-imposed thrombus.

was incontinent of urine and feces, and became progressively weaker. He died quietly on December 14, 19 days after entry and approximately five weeks after the onset of his illness. The chart of temperature, pulse, and respiration is shown in figure 3.

The clinical diagnoses were cerebral arteriosclerosis, cerebral hemorrhage with left hemiparesis, hypertensive and arteriosclerotic heart disease, and generalized arteriosclerosis.

Autopsy Findings: Autopsy was performed December 15, 1947, 29 hours after death.

The body was that of a 53 year old Negro male, measuring 70 inches in length and weighing approximately 140 pounds. There was no ankle edema, and the muscula-

ture was well developed. When the peritoneal cavity was opened, the subcutaneous fat was found to be decreased in thickness, and a small epigastric hernia containing omentum was noted. Examination of the brain revealed the vessels at the base to be sclerotic and tortuous, but patent throughout. A small area of softening, 3 by 2 by 1 cm., was found on the medial aspect of the right parieto-occipital region. A section of this area showed it to be dull, mottled red in color, and soft in consistency. The heart weighed 690 gm., and there was considerable hypertrophy of the myocardium of the left ventricle. The chambers showed moderate dilatation. The endocardium was smooth and glistening, except in the region of the left auricular appendage, where a firm, densely adherent mass, 3 by 2 cm. and 1 cm. in thickness, was found. Section of the mass revealed the portion adjacent to the auricular myocardium to be yellow-white in color and covered with a friable, easily separable, lamellated thrombus. The underlying portion was fused with the auricular endocardium, but it did not penetrate the myocardium. The adjacent auricular pericardium was smooth and glistening. The valves were thin, translucent, and free from vegetations. The coronary arteries

Fig. 5. Serial sections of the left auricular appendage. The tuberculoma appears white and the thrombus is darker in color.

showed moderate sclerosis, the lumen being narrowed and eccentric. The aorta showed moderate atherosclerosis with calcification. The right lung weighed 1,620 gm. and the left lung 760 gm. The former was boggy in consistency and the latter crepitant. On section, the lungs revealed innumerable miliary white nodules involving both upper lobes and the right middle lobe. A considerable quantity of pink, frothy fluid exuded from the cut surfaces of all lobes. The spleen weighed 230 gm. and showed a firm, yellow, projecting nodule, 1.5 cm. in diameter, which infiltrated and merged with the parenchyma to a depth of 2 cm. There was a hemorrhagic, wedge-shaped zone in the right kidney measuring 3 by 2 cm.

Microscopic Examination: The brain showed considerable tuberculous involvement of the pia arachnoid, with infiltration of the walls of the blood vessels. The area of malacia in the parieto-occipital region showed extensive caseation necrosis with tuberculous granulomatous reaction. Acid fast bacilli were found in all of these areas. Section of the heart showed marked hypertrophy of the myocardial fibers. The coronary arteries were sclerotic and calcified. In the region of the left auricular appendage, a tuberculoma was found intimately adherent to and infiltrating the endo-

cardium. The lesion (figure 6) showed caseation necrosis, epithelioid cells, fibrosis, round cell infiltration, Langhans' giant cells, calcification, and a small number of acid fast bacilli. Numerous miliary tubercles were found throughout all lung sections. There was some tuberculous involvement of the small arterioles of the lungs resulting in thrombosis. A few areas of bronchopneumonia with polymorphonuclear infiltration were seen. Miliary tubercles were found in the liver, spleen, adrenal, and kidney. The area of infarction in the spleen showed caseation necrosis and acid fast bacilli, and the one in the kidney showed simple necrosis.
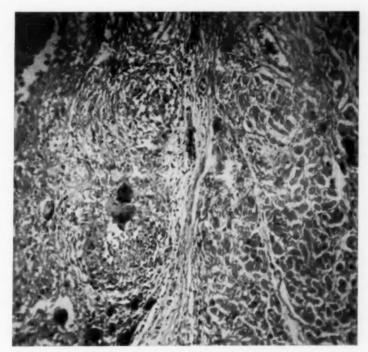
FIG. 6. Photomicrograph showing tuberculous granulation tissue in the endocardium of the left auricular wall. Tubercles do not invade the myocardium. The area beyond this point shows caseation necrosis. × 160.

From the nature of the tuberculoma in the left auricular appendage, showing calcification in some areas, it was apparent that this lesion was of long standing and preceded the generalized miliary tuberculosis. From the history, the infarcted area of the brain occurred five weeks prior to death. Similarly, it may be deduced that the infarcts in the spleen and kidney were of recent origin. It may then be inferred that the endocardial tuberculoma was the oldest active tuberculous lesion and acted as the seeding focus for the miliary tuberculosis and the embolic phenomena, the primary focus being no longer active. The areas of infarction in the brain and spleen were, undoubtedly, due to septic tuberculous emboli, while that of the kidney was probably a simple embolus.

COMMENT

Various possibilities as to the pathogenesis of this lesion have been propounded by various authors. The hematogenous route, whether by the coronary arteries or direct from the blood stream, is considered to be the mechanism by which the tubercle bacilli reach the endocardium.[1, 3] Retrograde lymph flow from the mediastinal lymphatics is favored by Rosenbaum and Linn.[5] Since the endocardium is avascular, the tubercle bacilli cannot be carried beyond the junction of the myocardium and endocardium. Inasmuch as early miliary tubercles and small tuberculomata are usually covered with endocardium[1] and appear to arise at the junction of the endocardium and myocardium, it may be concluded that the organisms were carried there by branches of the coronary arteries. Cases of tuberculous endocarditis have been reported as arising on previously damaged valves.[2, 4, 6, 8] Inasmuch as there is no intrinsic blood supply to the edge of these valves, tubercle bacilli can reach them in only one way, direct from the blood stream. Both hematogenous routes are possible, and there is no valid reason why one should be preferred to the exclusion of the other.

Coexistent miliary tuberculosis is found in most cases of endocardial tuberculosis. This is inevitable, when the tuberculoma is ulcerated, because innumerable tubercle bacilli are being shed into the blood stream. Frequently, the subendocardial tubercles are themselves miliary and are merely part of a generalized miliary tuberculosis.

There seems to be a difference of opinion as to the most frequent sites of involvement, the right ventricle[1, 10] or the right auricle.[9] It is felt, however, that an insufficient number of cases has been reported to warrant any statistical conclusions.

SUMMARY

A case is presented of endocardial tuberculoma of the right auricle, associated with miliary spread and septic infarction of the brain and spleen in a man with preëxisting hypertensive heart disease. The literature on tuberculosis of the endocardium is reviewed.

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LONGEVITY IN EXTENSIVE ORGANIC HEART LESIONS: A CASE OF LUTEMBACHER'S SYNDROME IN A MAN AGED 72 *

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An astounding feature of Lutembacher's syndrome is the ability of many patients to endure the marked lesion for many decades. One woman lived to the age of 74 [1] and passed successfully through 11 pregnancies and three abortions. In Bonnabel's report,[2] two patients lived to be over 70. It is difficult to document precisely the instances of Lutembacher's syndrome [3] in the literature. Many are included in reports upon interatrial septal defect without definite designation of the mitral lesion. An approximate enumeration would be as follows:

McGinn and White [4] reported 24; Roesler [5] mentioned 6 more; Tinney [6] in 1940 found 11 instances reported since 1934. A few additional case reports in the literature were not noted. Since then a number of individual reports have appeared.[7, 8, 9, 10, 11, 12, 13, 14] There are now in the literature probably between 50 and 60 cases proved by autopsy. In the absence of a central medical registry where cases may be assembled and analyzed, it is important that all cases encountered be available in the literature.

CASE REPORT

A 72 year old retired businessman was first seen at St. Vincent's Hospital on January 5, 1947, referred by Dr. Jack C. Cherry of Las Vegas.

Family History: The father died at 62 of miner's consumption; the mother died at 75 of pernicious anemia. There are three sisters living and well.

Past Medical History: Pneumonia three times; typhoid fever as a youth with superimposed pneumonia; repeated attacks of tonsillitis for which a tonsillectomy was performed at the age of 20 years; no history of rheumatic fever. Hemorrhoidectomy was performed seven years ago.

History of Present Illness: Fifteen years ago, after a few drinks at a convention, he had developed dyspnea on exertion. He was seen then by Dr. Cherry, who diagnosed auricular fibrillation. The dyspnea on exertion and the auricular fibrillation persisted, but he was able to continue work with restricted activity. Whenever he developed a cold the dyspnea became so marked he had to go to bed for a few days. After an attack of bronchopneumonia in 1941 he found it necessary to sleep on two pillows. Three years ago, in 1944, he developed abdominal swelling with ankle edema. He improved after the use of theophylline preparations. Since then he had taken one or two tablets daily. In October, 1946, he developed increasing dyspnea, orthopnea, a cough productive of mucopurulent sputum, insomnia, increased dependent edema, and ascites. There was no history of previous jaundice, gall bladder disease, or significant alcoholism. He had had no digitalis for several weeks but had received mercurial diuretics at intervals for the ascites and edema.

Physical examination revealed a moderately pale, slightly cyanotic, elderly dyspneic male. The thorax showed a moderate increase in the anteroposterior

diameter. The lungs revealed large and fine coarse crepitant râles, more at the left base posteriorly and a few at the right base. The apex beat of the heart was felt in the fifth interspace just outside the midclavicular line. The sounds were totally irregular, the rate being 110 per minute. There was a grade 3 systolic murmur at the apex with a questionable mid-diastolic component. There was roughening of the heart sounds over the precordium, but no true friction rub or thrill was palpable. The abdomen was distended and a fluid wave was present. The liver was smooth, slightly tender and enlarged three or four fingers'-breadth below the costal margin. Bilateral reducible indirect inguinal hernias were present. There was slight pitting edema in the right and left legs, and slight tenderness in the right and left calves, but Homans' sign was negative.
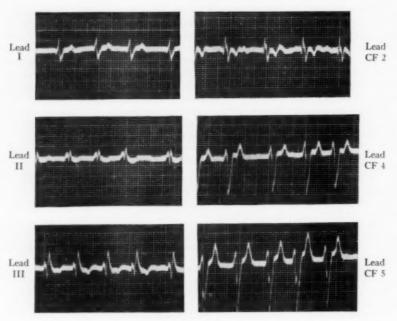
FIG. 1.

The tentative diagnoses were: (1) Arteriosclerosis of coronary arteries with auricular fibrillation and right and left ventricular insufficiency; (2) cardiac cirrhosis of liver; (3) bronchiectasis, left lower lobe; (4) benign prostatic hypertrophy; (5) indirect inguinal hernia, right and left; (6) possible adhesive pericarditis.

The patient was lethargic and apathetic. A nonprotein nitrogen level of 120 mg. per 100 c.c. of blood and a creatinine level of 4.2 mg. on January 6, 1947, was believed to explain his condition. The total protein of the blood was 10.2 gm., albumin 4.2 gm., globulin 6.0 gm. The icterus index was 32. An electrocardiogram revealed right bundle branch block with auricular fibrillation (figure 1). The clotting time of the patient was 38 seconds, that of the control 20 seconds; the Quick prothrombin concentration was 25 per cent. On January 8, a cephalin flocculation test in 24 hours

was 4 plus, in 48 hours, 4 plus. The blood count showed hemoglobin 15.5 gm.; erythrocytes, 4,560,000; leukocytes 7,800; lymphocytes, 6 per cent; monocytes, 3 per cent, and neutrophiles, 91 per cent. A urinalysis showed a specific gravity of 1.018, albumin 3 +, negative sugar and diacetic acid, many hyaline casts, an occasional leukocyte, no red blood cells. The nonprotein nitrogen level on January 8 was 200 mg. per 100 c.c. of blood; the creatinine level was 3.2 mg.

On January 9 the following note was made: "This morning, although the patient responds to questions, the objective evidence of increasing uremia has gone on apace. The patient twitches occasionally, not regularly, and there occur short periods of apnea. Over the precordium today, there is heard an intense squeaky leather (cri
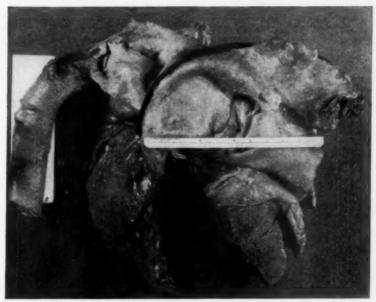
FIG. 2. Hypertrophy of the pulmonary artery. The smaller aorta, above and behind the pulmonary artery, has been opened in its ascending portion.

de cuir) type of pericardial rub. It is of optimal intensity just above and medial to the nipple and peculiarly, is heard high in the axilla near the anterior axillary fold." The nonprotein nitrogen level was 85.7 gm. and the creatinine level was 1.2 gm. On January 10 the nonprotein nitrogen level was 60 mg. Despite the apparent improvement in the azotemia, the congestive failure increased and the patient died at 1:05 a.m. on January 11, 1947.

A necropsy was performed by Dr. James E. Kahler. The heart weighed 840 gm. The pulmonary artery was very large, much larger than the aorta (figure 2). There was great hypertrophy and dilatation of the right ventricle. There was a large inter-auricular septal defect present, the lower edge of the defect lying over the mitral and tricuspid valve (figure 3). There was dilatation of both auricles, but no thrombi were found in the auricles or auricular appendages. The aortic, tricuspid and pul-

monary valves showed a slight degree of atherosclerotic change. The mitral valve
was fish-mouth in type, markedly stenotic and fibrous, and partly calcified (figure 4).
The coronary arteries showed grade 2 sclerosis, were quite large and patent, and
showed no thrombosis. The myocardium revealed no areas of infarction.

The liver weighed 1,500 gm. and was dark reddish brown in color. Microscopic
examination showed a complete reversal of the normal architecture of the liver in
that the portal triads stood in the center of a ring of liver tissue which was surrounded
by a fairly wide zone of fibrosis. The reversed lobulation was very well demonstrated
here and was considered diagnostic of cardiac cirrhosis.

DISCUSSION

This patient showed all the essential findings for the Lutembacher syndrome.
Associated with the interatrial septal defect were marked dilatation and hyper-
trophy of the right side of the heart and dilatation of the pulmonary artery ex-
ceeding the size of the aorta. Marked stenosis of the mitral valve was present.
The failure to diagnose the condition before death was due to the absence of
significant murmurs and to failure to obtain a roentgenogram of the heart. The
systolic murmur at the apex was attributed to left ventricular dilatation, and
the mid-diastolic component was questionable and was not considered significant.
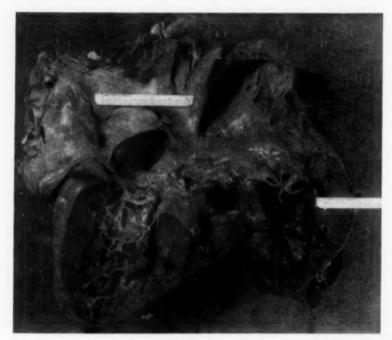
FIG. 3. Right heart showing interatrial septal defect just above the tricuspid valve. Note
hypertrophy of right heart muscle.

Fig. 4. Interatrial septal defect overriding the mitral valve. Thickening of the mitral leaflets and shortening and thickening of the chordae tendineae are shown. Marked stenosis of the valve orifice is poorly demonstrated because of the manner in which the chambers are held open to demonstrate the septal defect.

An interesting point was the appearance of the peculiar adventitious sound, the timbre of which was that of the squeaky sound of new leather heard at times in fibrinous pericarditis. This may have been a reflection of abnormal eddies or currents in the heart stream produced by the lesion. The extreme azotemia was interesting. The nonprotein nitrogen of 200 mg. per 100 c.c. of blood is one of the highest figures we have seen in extrarenal azotemia due to congestive heart failure. The period of 15 years during which the patient was able to conduct his business with limited activities in the presence of chronic auricular fibrillation is amazing. The average length of life in a patient with rheumatic heart disease who develops established auricular fibrillation is about two and one-half years. Yet in this middle-aged individual of 57, with mitral stenosis and inter-auricular septal defect, life continued despite established auricular fibrillation for 15 years.

SUMMARY

An instance of interauricular septal defect with mitral stenosis is reported in a man who lived to the age of 72 and remained active in business until a few months prior to his death. The ability of the heart in certain individuals to compensate for certain extensive mechanical defects and to allow life to continue to a normally expectant age is pointed out.

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AN UNUSUAL COMPLICATION FOLLOWING THYROIDEC-
TOMY: HEATSTROKE WITH PERMANENT
CEREBELLAR DAMAGE *

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THYROIDECTOMY for hyperthyroidism today carries with it a low mortality and infrequent complications. The medical complications following thyroidectomy are well known and, with the use of iodine and antithyroid drugs, they have been reduced to a minimum. Thyroid crisis is rarely seen today. The incidence of tetany, myxedema, and recurrence of hyperthyroidism are complications which are becoming less frequent. We have recently encountered an unusual type of complication following thyroidectomy which, as far as we can determine, has not been previously reported. The patient was suffering from hyperthyroidism and a subtotal thyroidectomy was performed. Two days later, following a transfusion, she developed heatstroke and, subsequently, permanent cerebellar damage. This thermal complication, which may occur in other surgical procedures, we believe to be of sufficient interest to merit reporting.

CASE REPORT

First Admission: The patient was a 39 year old Negro female who was admitted to the Staten Island Hospital on May 13, 1944, because of increasing nervousness, weakness, and loss of weight of several months' duration. The patient was born in the British West Indies and, except for mild bronchial asthma, had always enjoyed good health. She was previously admitted to this hospital in February, 1942, for the uneventful normal delivery of her fourth child.

Physical examination disclosed an ambulatory, apprehensive patient with some prominence of her eyeballs and an obvious fullness in her neck region. Her general development was good, but there was evidence of recent loss of weight. Her rectal temperature was 99° F. The pulse rate averaged 120 per minute. The blood pressure measured 140 mm. Hg systolic and 80 diastolic. The thyroid gland was diffusely enlarged with somewhat more prominence of the left lobe. A loud bruit was heard over the entire thyroid region. The heart was not enlarged. The heart sounds were loud and regular; a grade II systolic blowing murmur was heard over the base of the heart. The lungs were normal to auscultation, and examination of the abdomen disclosed no abnormalities. A neurologic examination was not remarkable except for a moderate regular tremor of the outstretched fingers.

The laboratory workup included basal metabolism studies which were reported as plus 88 per cent and plus 80 per cent. A hemoglobin determination was 70 per cent (Sahli) and the red cell count was 3.65 million per cu. mm. The white cells were 4,700 per cu. mm., with a normal differential. An uncatheterized urinalysis showed a faint trace of albumin, negative reaction for sugar, a specific gravity of 1.024, and normal microscopic findings. The nonprotein nitrogen of the blood was 35 mg. per cent, and the fasting blood sugar, 83 mg. per cent.

A diagnosis of diffuse toxic goiter was made and the patient was prepared for surgery. She was given 10 minims of Lugol's solution, and 0.03 gm. of phenobarbital three times a day. In addition, a high caloric diet and ferrous sulfate were prescribed. Under this regimen her general condition was strikingly improved. She gained weight, her basal metabolism dropped to plus 40 per cent and her pulse averaged 90 per minute.

On May 31, 1944, 18 days after admission, a subtotal thyroidectomy was performed by Dr. Frederick Coonley. Avertin, supplemented by nitrous oxide and ether, was the anesthetic employed. Her immediate postoperative condition was considered satisfactory by both the anesthetist and the surgeon, although the next day her temperature rose to 102.5° F. (rectal), and the pulse varied from 150 to 170 per minute. On the second postoperative day her temperature kept increasing and, despite alcohol sponges, her temperature at 2 p.m. rose to 105° F. (rectal). Lugol's solution was administered and fluids were encouraged. At this time she was observed to be rational and coöperative. At 6 p.m. a transfusion was attempted. The patient's blood type was O, and a compatible donor of the same type was used. The transfusion was administered slowly and within a half hour of the onset, when approximately 300 c.c. had been taken, the patient experienced a severe chill and the transfusion was discontinued. She soon became irrational and attempted to get out of bed. At 6:30 p.m. the breathing was labored and the rectal temperature was noted to be 108.4° F., the pulse 200, and the respirations 50 per minute. The patient was immediately given alcohol sponges, and ice packs were applied to the body. Within an hour, the temperature was 106.8° F. (rectal) and the pulse 158 per minute. At 10:20 p.m. "involuntary tremors of the head and upper extremities" with "eyes rolling about uncontrollably" were noted. The patient soon lapsed into a semicomatose state, thrashed about, was incontinent, and continued to show tremors as described. She remained in this state for 24 hours and then suddenly broke out in a profuse diaphoresis followed by a drop in her temperature reading to 101° F. (rectal). Al-

though the patient was now sweating profusely, it should be mentioned that at the height of her fever the skin over her entire body was remarkably dry and devoid of moisture. She was seen by a medical consultant who noted marked dullness, bronchial breathing, and some moist râles over the right lower chest posteriorly. A diagnosis of pneumonia or pulmonary embolus was entertained and penicillin therapy was commenced. The patient, however, failed to show any definite improvement, and the temperature remained elevated but at a lower level. In the meantime, ill-defined twitchings of the head, nystagmus, and gross irregular tremors of all extremities were now becoming manifest. A spinal tap was performed, and the appearance, pressure, cell count, chemical findings and serology were normal. Repeated urinalyses showed a trace of albumin with occasional granular casts and a few red cells. The white count averaged 12,000 cells per cu. mm., with 85 per cent polymorphonuclear cells. There was a secondary anemia with a hemoglobin of 56 per cent (Sahli). The icterus index was 9 units and the blood calcium was 9 mg. per cent. Blood cultures revealed no growth.

The patient ran a stormy course (figure 1). On the sixth postoperative day she developed decubitus ulcers which became infected, and two weeks later she developed a thrombophlebitis of the left saphenous vein. Both these complications were completely healed by the time of her discharge from the hospital. The patient was discharged from the hospital on September 30, 1944, the one hundred nineteenth hospital day, and at that time it was noted that there was evidence of an intention tremor, incoördination, and some ataxia. It is interesting to note that, although the patient was developing a profound neurologic disturbance, attention was not seriously directed to this condition until the acute symptoms had subsided. The following is a note by the neurologist six weeks after the operation: "There is weakness of the right forearm with moderate hyper-reflexia—appears to be central in origin. She has some speech difficulty, but is not aphasic. Abdominal reflexes are absent. Lower extremities show hyper-reflexia—equal, but no Babinski. She has some twitching of the angle of her mouth. Pupils are equal; optic fundi negative. Impression: Cerebral thrombosis."

Second Admission: The patient was not seen again until June 1, 1946. Since the operation for the thyroidectomy two years previously, she was finding it difficult to walk unaided and her speech was becoming progressively impaired. In addition, there were marked tremors of the hands and head. Examination disclosed a helpless invalid and the important findings were limited to the neurologic examination (Dr. Samuel Reback): "The patient shows a profound involvement of the cerebellar lobes. There is marked decomposition of movements in performing finger-to-nose tests bilaterally. There are positive rebound and check phenomena and adiadokokinesis. In the lower extremities she shows marked ataxia; heel-to-knee test performance is almost impossible. There is some hyperactivity of the deep reflexes except for an absent ankle jerk on the left. She has definite dysarthria, with pulling over of the uvula and soft palate to left indicating weakness of the right tenth nerve. She has a positive Babinski on the right with atrophy of the right calf. The coarse tremor of the head is also cerebellar. The' rest of neurological examination including the fundi is normal."

A spinal tap again disclosed perfectly normal findings. The blood cholesterol was 141 mg. per cent and the blood calcium 11.7 mg. per cent. Except for a moderate secondary anemia the blood count was normal. Repeated tests for sickling of the blood disclosed no evidence of this abnormality. The blood Wassermann test was negative. Several basal metabolism studies were performed, and the average reading was plus 15 per cent. Because of the tremor it was difficult to interpret the electrocardiogram, but it was thought to show low T-waves in all leads. A roentgen-ray study of the skull was not remarkable.
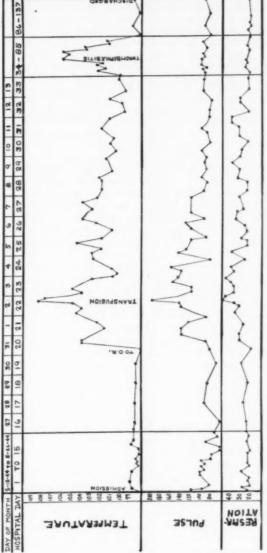
FIG. 1. Temperature chart of patient during first hospital admission.

During her stay in the hospital, the patient developed an infection of her upper respiratory system. Her temperature rose abruptly to 106.4° F. (rectal). In spite of this high temperature her general condition was good. Sweating over the general body surface was noted. Penicillin was administered in adequate doses and the infection subsided in a few days without incident.

Because of the stationary nature of her illness the patient was transferred to a chronic hospital. The following abstract was received from Bellevue Hospital, dated December 8, 1947: "The above named patient was here from August 29, 1946, to November 11, 1946. She was given a work-up in Psychiatric Division where the diagnosis was felt to be probable cerebellar pyramidal and extrapyramidal degeneration of unknown etiology; she was then transferred to the General Hospital. Electroencephalogram was reported as probably normal. Blood and urine were normal and lumbar puncture was negative. Her condition was unchanged on discharge."

DISCUSSION

The normal body temperature is maintained by a delicate balance between heat production and heat loss. The mechanism is complex and is probably integrated in the hypothalamus. In thyrotoxic crisis ("thyroid storm"), this thermoregulatory mechanism is labile and in certain instances may break down completely. The fundamental pathologic physiology of thyrotoxic crisis is unknown, and a combination of many factors probably contribute to the hyperpyrexia of this syndrome. Usually because of the dramatic and sudden nature of a crisis, attention is directed to the circulatory features of this condition. Actually, the thermal response may be more critical for, if the temperature becomes uncontrollable and rises above 106° F., heatstroke may ensue with devastating and irreversible damage to the brain and other vital organs.

The increased metabolism resulting from a high fever enters into a vicious cycle and is of more than theoretic interest. In a borderline hyperthyroid state, it may be sufficient to throw a patient into an alarming toxic state. It has been shown [6] that for each degree (Fahrenheit) rise in body temperature, there is an elevation of between 5 to 14 per cent in the metabolic rate, and as the temperature rises above 106° F., the metabolic rate increases even more sharply. In animal experiments, [3] warming the carotid body 3 to 4° Centigrade above normal temperature resulted in 33 to 70 per cent increase in respiratory volume.

We are not prepared to state that the chain of events seen in our patient was fundamentally one of thyrotoxic crisis. In active thyroid clinics, [5, 7] where many thousands of operations for thyroidectomy have been performed, the type of complication seen in our patient has never been encountered. The patient received a blood transfusion on the day her temperature was on the rise (105° F., rectal—figure 1), and, following the transfusion, there was a chill and a further elevation in temperature to the almost unbelievable height of 108.4° F. There is little doubt that this transfusion aggravated the thermal reaction. The blood was described as compatible, but unfortunately a detailed report of the hematologic workup was not available for review. The citrate method was used, and pyrogenic reactions are encountered not infrequently with this technic if sterilization is not exact. There was no clinical or laboratory evidence to indicate that the patient had a hemolytic reaction.

It is of interest to note that on the day of operation, and for two days thereafter, Staten Island was experiencing a heat wave. The official weather bureau records are only partly revealing. The nurses attending our patient re-

call that on the day of the operation the poorly ventilated ward where the patient was hospitalized was unbearably hot and humid.

The late neurologic complications of heatstroke have not been stressed sufficiently. In a recent study of 125 fatal cases of heatstroke, Malamud, Haymaker, and Custer [8] found that some of the most consistent and striking changes observed at post mortem were those in the central nervous system, particularly the cerebellum. To quote [8]: "We regard the irreversible damage to the central nervous system as seen in our cases as adequate pathologic basis for the cerebellar and mental sequelae which have been reported in nonfatal heatstroke." This susceptibility of the cerebellum to extreme heat has been noted by others.[1, 4, 9]

The muscular disturbance seen in our patient was at first confusing. One medical consultant considered the possibility of a calcium deficiency, but determinations from this standpoint were normal. She developed some mental aberrations and for a time a diagnosis of hysteria was entertained. In view of the widespread damage found in the brain of patients dying from heat pyrexia, it is not surprising that bizarre psychiatric and neurologic manifestations occur.

A fever is ordinarily considered a symptom and is not treated per se. In patients under observation for thyrotoxicosis, however, a fever, regardless of its etiology, has serious implications. For these patients heroic antipyretic measures should be available,[2] as heatstroke is a distinct possibility. In certain instances, fatalities in thyrotoxic crisis may be explained on this basis.

SUMMARY

1. An unusual complication following thyroidectomy for a diffuse toxic goiter is presented. Two days following the operation, and after a transfusion, the patient developed a fever of 108.4° F. and manifested soon thereafter profound cerebellar damage.

2. The late neurologic sequelae of heatstroke are emphasized. Patients experiencing severe thermal reactions should be followed closely for late cerebellar changes.

3. A high fever in a patient under observation for thyrotoxicosis, regardless of its etiology, has serious implications.

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DISSEMINATED LUPUS ERYTHEMATOSUS WITH SYDEN-HAM'S CHOREA AND RHEUMATIC HEART DISEASE: REPORT OF A CASE WITH AUTOPSY *

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IT has been established in recent years that both rheumatic fever and disseminated lupus erythematosus are systemic disease entities characterized by lesions involving certain peripheral and central vascular fields. The lesions are similar to those produced in experimental anaphylaxis. Klinge[1] demonstrated that these "rheumatic" granulomas, formerly thought to be specific for rheumatic fever, are neither specific nor constant. In rheumatic fever the predominant rôle of streptococci as allergens is undisputed. However, it has also been established that various nonbacterial agents are capable of producing similar characteristic morphologic changes as seen in various disease entities, including rheumatic fever and disseminated lupus erythematosus.

Chorea is considered by most reputable observers as a manifestation of rheumatic fever. Such experienced observers as Baehr and Pollack[2] have never seen the simultaneous occurrence of both rheumatic cardiac disease and disseminated lupus erythematosus. They admit, however, that in persons who have once had acute rheumatic carditis there may sometimes develop disseminated lupus years later.

So far, Sydenham's chorea has not been observed in association with disseminated lupus erythematosus. The simultaneous occurrence of Sydenham's chorea, rheumatic heart disease, and disseminated lupus erythematosus in one patient warrants the following report.

CASE REPORT

A 16 year old Negro schoolgirl entered the hospital on September 7, 1947, with the complaint of constant uncontrollable muscular activity of 10 days' duration. From the age of six years she had had frequent sore throats and joint pains. Eight months prior to entry she developed a sore throat and arthralgia, with marked swelling and heat in both elbows and in the knees and ankles. The arthralgia lasted three weeks. A diagnosis of rheumatic fever was made by a private physician. The patient was placed on limited physical activity. Three weeks before entry she developed a red macular rash on both palms and pain in the metacarpophalangeal joints. The rash lasted 10 days and was followed by a severe sore throat and uncontrollable twitchings of the facial muscles, which in three days spread to all extremities and were so severe that they interfered with eating, talking and sleeping.

Past History: Measles in early childhood.

Family History: Entirely noncontributory. There were no allergic diseases in her family.

On physical examination the patient appeared to be well developed and well nourished. She was in no acute distress but exhibited constant uncontrollable and purposeless movements. Temperature 99° F.; respirations 24 per minute; pulse 100;

blood pressure 110/60 mm. Hg. There was widespread increased neuromuscular activity involving the face and all extremities. This was so severe that it interfered with talking and even the most simple movements. Rapid involuntary and unrhythmical twitching movements involved the face and upper extremities. There was marked weakness, ataxia, and asynergy. The fundi were not adequately visualized because of random movements. The patient was alert, coöperative, and oriented, but appeared emotionally labile, talking and crying intermittently.

Laboratory: Hemoglobin 12 gm.; red cells 4.2 million; hematocrit 31; white cells 5,200; neutrophiles 56 per cent; lymphocytes 34 per cent; monocytes 5 per cent; eosinophiles 4 per cent; basophiles 1 per cent. Sedimentation rate, 32 mm. per hour. Urinalysis and Wassermann tests were negative. A chest roentgen-ray was within normal limits, as was an electrocardiogram.

A diagnosis of rheumatic fever with Sydenham's chorea was made. The patient improved on bed rest until September 20, 1947, when she had fever of 104° F. and epistaxis. She was found to have marked cervical and inguinal adenopathy and a palpable spleen. There was leukopenia with 3,200 leukocytes, 21 per cent neutrophiles, 16 per cent stabs, 50 per cent lymphocytes, 8 per cent monocytes, 3 per cent eosinophiles, and 2 per cent basophiles. The urine was entirely normal. Blood cultures and agglutinations for typhoid, paratyphoid, and heterophile antibodies were negative. Stool examinations were also entirely negative. The patient maintained a daily temperature of 102 to 104° F. for one week. She gradually became afebrile but her emotional instability, slight choreiform movements, lymphadenopathy, leukopenia, and splenomegaly persisted. She was discharged one month after admission afebrile and without clinical evidence of chorea. The lymphadenopathy and splenomegaly had disappeared.

Six weeks later the patient reëntered the hospital because of dull aching precordial pain and arthralgia of the left elbow and hand of three days' duration. Temperature 102° F.; pulse 118; blood pressure 116/65. There was marked emotional instability and apprehension, but no choreiform movements were present. The pharynx was injected and the tonsils were cryptic and enlarged. There was marked submandibular adenopathy. Gallop rhythm was present but no murmurs were heard. There was no joint tenderness or swelling. Hemoglobin was 11 gm.; red cells 4.9 million; mean corpuscular hemoglobin 22. There were 3,950 lymphocytes, 6 per cent monocytes, 1 per cent eosinophiles. The platelets appeared normal. There was no sickling. There were hypochromasia and anisocytosis. The urine contained a trace of albumin. Blood cultures, agglutinations, and a chest roentgen-ray were all negative. Tuberculin skin test in 1:10,000 dilution was negative. The patient was placed on sodium salicylate, 2.0 gm. three times daily. The fever promptly subsided. An electrocardiogram revealed an auricular and ventricular rate of 110, normal electrical axis, P–R interval of 0.16 second, QRS 0.08 second, T waves upright in Leads I and II, inverted in III. It was interpreted as sinus tachycardia.

Three days later she again had epistaxis, and a grade 2 systolic apical and a grade 1 diastolic apical murmur were heard. A systolic thrill was felt at the apex. A maculopapular rash was noted on the anterior surfaces of both legs. Salicylates were discontinued on appearance of the rash, and the temperature promptly rose to 102° F. This was followed two days later by a violaceous erythema in butterfly distribution over the nose and malar eminences (figure 1). The diastolic murmur was still present. A diagnosis of disseminated lupus erythematosus was made.

Subsequently, a large ulcerating lesion of the hard palate with a dirty gray membrane was noted. Repeated cultures were negative for diphtheria organisms. The temperature remained around 103° F., and treatment with penicillin and pyribenzamine was begun. This was kept up for several days but was discontinued when no benefit from it was noted. During the next 10 days the rash spread to involve

the thighs, and red macules were noted on the palms, the thenar eminences, and the finger tips. The cuticular margins showed tender, red macules with beginning ulceration. Now for the first time the fundi were found to contain white "cotton-wool" type exudate, which varied between one-quarter and one-half disc in diameter. The retinal vessels were congested but there was no papilledema. A few pinpoint hemorrhages were noted. Gallop rhythm was present, as was the systolic apical murmur, but the diastolic murmur could not be heard. The spleen edge was palpable

Fig. 1.

4 cm. below the costal margin. There were 3,200 leukocytes and moderate reduction of the platelets. The urine now contained albumin, many fine granular casts, and a few red cells. The blood nonprotein nitrogen was 22 mg. per cent. Four days later the diastolic murmur was again heard. The rash had spread to involve the entire body, with the exception of the chin. A skin biopsy was taken from the forearm and revealed an atrophic, hyperkeratotic epidermis. The basal cells of the epidermis showed colliquative degeneration; the papillary cutis was sclerotic and homogenized.

There was slight lymphocytic perivascular infiltration around the vessels of the lower cutis. The superficial vessels were dilated and the collagen of the fibrous connective tissue showed granular degeneration (figure 2). The electrocardiogram revealed a rate of 100, sinus rhythm, a P–R interval of 0.16 second, and T_1, T_2, and T_4 were low; R was small in all precordial leads. T waves were inverted in $CF_{1, 2, 3 \text{ and } 4}$, upright in $CF_{5 \text{ and } 6}$. The tracing was interpreted as showing sinus tachycardia, right axis deviation, and being suggestive of pericardial or myocardial disease. There was a reversal of the albumin-globulin ratio (3.9/4.1 gm. per cent). There were 2,800 leukocytes and a marked thrombocytopenia. Sedimentation rate was 28 mm. per hour.
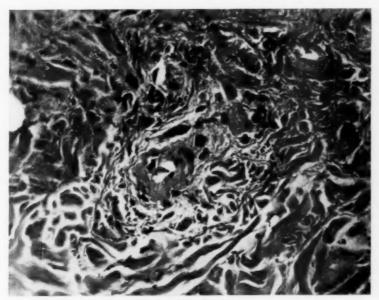
Fig. 2. Skin biopsy from arm. × 450. See text for description.

Over a period of the next four weeks the patient became increasingly irritable. She was now assaultive, resistive and unresponsive. Her general motor responses were slow and meaningless and were interspersed with aimless gestures. Her speech was slow and irrelevant and showed a hallucinatory and delusional trend. It was necessary to seek closed placement for her care. At this time no choreiform movements were present. Her rash had subsided and she was afebrile. The blood pressure remained around 100/60.

Examination three months after the appearance of the characteristic picture of disseminated lupus erythematosus revealed her to be markedly emaciated. There was a coarse, branny desquamation over the entire body, most marked on the face and limbs. There was a pigmented area of butterfly distribution over the nose and malar eminences. The base of the nail beds and cuticular margins showed healing ulcerated areas. A grade 2 systolic apical and a grade 1 diastolic apical murmur were present.

There was cervical, epitrochlear and inguinal adenopathy. The spleen could not be felt. Speech was unintelligible, echolalic and neologic. Random uncoördinated movements were present and little coördination was shown. Orientation, insight and judgment were lacking, and the patient appeared childish and completely out of contact. It was felt that the patient had disseminated lupus in remission with a psychosis secondary to cerebral vascular damage.

Her psychotic symptoms cleared to a considerable degree and she became afebrile. However, on April 15, 1948, she developed fever of 102° F. The skin rash recurred and there was bleeding from the gums and nares. She was transferred to the Los Angeles County Hospital with signs and symptoms of bilateral bronchopneumonia and died on April 28, 1948.

Autopsy was performed about four hours after death by one of us (E. B. C.), the report of which reads, in part, as follows:

External: The body is that of a well developed, thin, 17 year old Negress weighing 31.7 kg. and measuring 165 cm. in length. There is a prominent hyperpigmented butterfly rash over the face, and a marked eruption is present over the lower and upper extremities, particularly over the extensor surfaces. Scattered over the torso there are numerous hyperpigmented areas. There is a small decubitus ulcer over the sacrum and erosion of the skin over the right buttock. There is clotted blood in the nares. The lips are covered with a small amount of dry blood. The mucous membranes are pale, as are the nailbeds.

Skull and Central Nervous System: Meninges are smooth and glistening. Vessels show no atherosclerosis. There are no malformations. Brain weighs 1,010 gm. It looks rather small for a girl of 17. Convolutions are also rather narrowed; however, no widening of the sulci is found, and the cisterns at the base are not notably prominent, except for the cisterna magna. The cerebral hemispheres are cut in a series of frontal sections. The cortex of the frontal lobes seems thinner than average, especially along some of the deeper sulci. The lateral ventricles are perhaps slightly larger than average but not excessively so. The same is true of the third ventricle. The basal ganglia, paying particular attention to the lenticular nucleus, discloses no gross alteration from normal; otherwise, sections through the cerebral hemispheres are not remarkable. Section of the brain stem and cerebellum presents no unusual findings.

Neck Organs: The thyroid is of normal size and has a pink color on cut section. It appears grossly normal.

Cardiovascular System: The pericardial sac is smooth and glistening and contains 300 c.c. of straw-colored fluid; specific gravity is 1.018. The heart weighs 250 gm. The right ventricle is dilated, as is the right atrium and right auricular appendage. The valves measure: mitral 9.5 cm., aortic 5 cm., pulmonic 6 cm., and tricuspid 11 cm. The mitral valve has nodular thickenings, and on the septal leaflet there is a small healed verruca; the mitral ring admits two fingers; the chordae tendineae are thickened. The tricuspid valve is likewise thickened; its chordae tendineae, however, are not abnormal. The aortic and pulmonic valve leaflets are normal. There are two subendocardial petechial hemorrhages in the right atrium just above the tricuspid valve orifice. The coronary arteries are patent throughout. The myocardium, on cut section, is pale brown in color and contains small gray areas throughout the septal and left ventricular wall. The left ventricular wall measures 9 mm., the right, 5 mm. The aorta contains a minimal amount of atheromatous changes.

Respiratory System: The pleural surfaces are disturbed by a minimal amount of acute fibrinous exudate. The left pleural space contains 600 c.c. of straw-colored fluid; specific gravity is 1.020. The left lung is adherent to the diaphragm; the right is completely free. The left lung weighs 320 gm.; it is crepitant but slightly con-

gested at the base. On cut surface there are scattered areas of hemorrhage; the basal portions are congested. The right lung weighs 390 gm.; its appearance is similar to that of the left lung. On cut surface it likewise shows these hemorrhagic areas and at its base is also congested. Tracheobronchial lymph nodes are somewhat enlarged, the largest measuring 3 by 4 cm. and, on cut surface, is a gray-white color, with scattered areas of anthracotic pigment. The tracheobronchial tree is patent throughout; the mucosa seems injected in the larger divisions of the bronchi. The vessels show no atherosclerosis; they are patent throughout and contain no thrombi.

Digestive System: The peritoneal cavity contains approximately 150 c.c. of straw-colored fluid. The peritoneum is smooth and glistening. The stomach, esophagus, and duodenum are normal throughout their lengths. In the mesentery and omentum there are scattered pink nodes of varying size. The intestine, large bowel, and rectum appear normal. The pancreas appears to be of normal size; on the cut surface it is yellowish gray and normal lobular pattern is retained. The pancreatic duct is patent throughout its length.
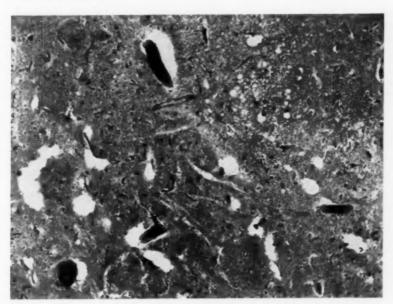
Fig. 3. Brain. × 85. Note area of softening and vascular occlusion by thrombi.

Hepatic System: The liver weighs 1,400 gm. and is pale brown in color. On cut surface the normal lobular pattern is seen. Its lower border is 2 cm. below the costal margin. The gall bladder, bile ducts and portal system are normal.

Spleen and Lymphatic System: The spleen weighs 140 gm. Its diaphragmatic surface is adherent to the diaphragm and to a portion of the left lower lobe of the liver by thin, easily separated, fibrinous bands. The capsule is thickened in areas and in certain portions is calcified. On cut surface the malpighian bodies are exceedingly prominent and the spleen is firm. Lymph nodes of the mesentery and the tracheobronchial tree, as noted above, are enlarged; peripheral lymph nodes do not appear abnormal.

Urinary Tract: The kidneys weigh: left, 180 gm.; right, 160 gm. Superficial vessels are prominently dilated and give the kidney a mottled appearance. These vascular dilatations occur particularly on slight depression, whereas there are slight elevations in the cortical surfaces, which are of yellowish color. There are occasional petechial hemorrhages scattered particularly in the left kidney. The capsules strip with ease. On cut surface the kidneys are pale. Cortical markings are prominent, but the cortex is diminished in thickness. Peripelvic fat is edematous and is increased in amount. Pelves and ureters are normal, as in the urinary bladder. Postmortem blood creatinine is 2.8 mg. per 100 c.c.

Genital System: The cervix, uterus, tubes, and ovaries are normal.

Endocrine System: The pituitary and thyroid appear grossly normal. One parathyroid is enlarged. Suprarenals are of normal size and are grossly normal.

Skeletal and Muscular Systems: Not remarkable.

HISTOPATHOLOGY

Brain: Sections through the cortex and lenticular nuclei disclose the presence of small vascular changes of the small blood vessels in the form of proliferation, apparently of the intimal structures. The blood vessels appear to be thicker-walled than usual. In some areas of the cortex there are infarctions, with occlusion of the vessels by thrombi (figure 3). In the lenticular nuclei the same changes are to be found. In addition, however, there are also deposits of iron in the small vessels of the globus pallidus. This is most marked on one side. Moreover, there is, in certain areas, what appears to be a most acute inflammatory condition, characterized by the presence
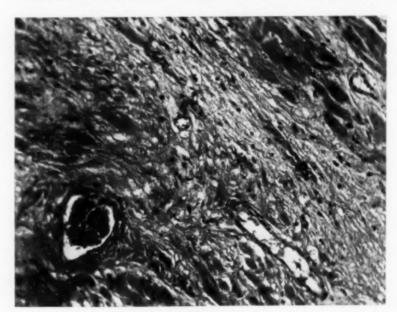
FIG. 4. Myocardium. ×150. Note basophilic hyaline stroma, fibrous connective tissue replacement and thrombosed vessel.

Fig. 5. Endocardial verruca. × 150.

of leukocytes about many of the regional vessels. There is also some associated softening of the gray matter of the lenticular nucleus.

Heart: Valve: At the root of the valve there is an abundant basophilic staining material. In some areas there are masses of fibrin; in others, small verrucae with fibrin, platelets, mesenchymal cells, and some polymorphonuclear and large mononuclear cells. The mitral valve is thickened, as are the chordae tendineae, and show whorled proliferations of fibroblasts.

Pericardium: Hyalin basophilic thickening is present with infiltration by leukocytes. There is subpericardial reaction of myocytes and monocytes and necrosis within the pericardial thickening.

Myocardium: There are patchy areas of fibrous replacement of the muscle fibers. The interstitial stroma is finely reticulated and basophilic with scattered areas of large amounts of basophilic staining material. The larger arterioles show moderate thickening of the media. The intimal cells are swollen and increased in number. Many of the medium and smaller arterioles are occluded by hyalin thrombi. Some of the thrombi are organized; an occasional one is of recent origin with piling up of platelets. Some capillaries show hyalin thickening of the walls. Around the arterioles, especially those containing thrombi, there is a zone of basophilic edematous stroma (figure 4). There are also masses of indefinite granular eosinophilic material with myocytes in and around it. There are many myocytes scattered throughout the muscle. There are some old fibrotic nodules interpreted as late Aschoff bodies. The auricular mural endocardium shows a thick sessile verruca composed of basophilic hyalin material infiltrated by numerous polymorphonuclear and some mononuclear cells (figure 5).

Lymph Node: Follicles are smaller in size and fewer in number. Marked congestion of the sinusoids and some increased reticulum. Lymphoid tissue is scanty and the vessel walls contain hyalin deposits.

Skin: See biopsy report above.

Thyroid: Diminished colloid. The colloid present is thin.

Spleen: Congestion of the pulp. The penicillary arteries show concentric reduplication of the wall, giving an "onion peel" appearance. Within the sinusoids are large mononuclear cells and a few plasma cells (figure 6).

Kidney: Architecture is well preserved. Some of the vessels show "peculiar" smudging. The tubules are slightly dilated and contain granular casts. Glomeruli show thickening of the basement membrane of the capillary loops. Many of the capillary tufts show definite "wire loop lesions."

Most of the arterioles are fairly well preserved. A few show thickened walls with swelling and proliferation of endothelium (figure 7).

Liver: Slight fatty metamorphosis. Slight increase of periportal fibrous tissue.

Lung: The pleural surfaces show deposit of fibrin beneath which is a layer of degenerating polymorphonuclear and other inflammatory cells. The pleural cells are converted into a row of irregular cuboidal cells. The connective tissue beneath this layer shows fragmentation and separation of the collagen fibers by basophilic material. Some areas of the lung show alveoli filled with macrophages, red cells, and moderate numbers of polymorphonuclear cells. Other areas show organizing pneumonia and pulmonary edema. A few vessels show change similar to that described in the kidney and heart, and some contain hyalin thrombi. There is acute bronchitis.

Ovaries: Congestion of blood vessels; otherwise no significant lesion.

Uterus and Cervix: No significant lesion.
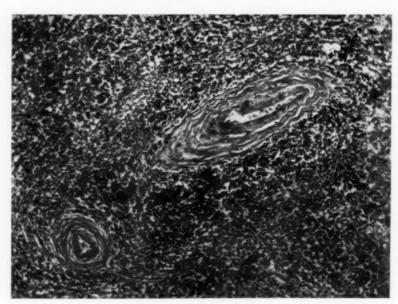
Fig. 6. Spleen. × 110. Note the "onion peel" appearance of the vessel wall.
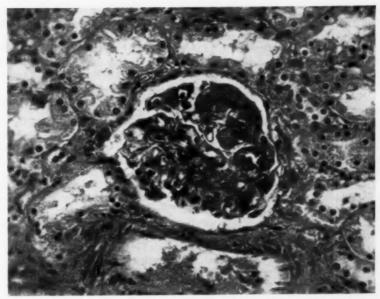
Fig. 7. Kidney. × 300. Note hyaline thrombi in the capillaries and thickening of the capillary walls.

Psoas Muscle: Small collection of lymphocytes.
Bladder: No significant lesion.
Adrenal: Slight hyalin thickening of the walls of arterioles.
Pancreas: No significant lesion.
Bone Marrow: Normal bone trabeculae; hyperactive cellular marrow.

DISCUSSION

The pathologic features of disseminated lupus erythematosus consist mainly of connective tissue changes in the walls of the small arteries. In the affected areas there are swelling of the connective tissue ground substance and fibrinoid degeneration of collagen fibrils. Fibrinous degeneration of collagen and subsequent vasculitis can occur both as a general and as a local expression of injury in a variety of heterogeneous processes. The changes seen in disseminated lupus erythematosus, periarteritis nodosa, rheumatic fever, and serum sickness are due to an allergy produced by specific immunity processes. It seems well to point out that the allergens acting in these diseases may be of nonbacterial origin and do not even have to be proteins. Sulfonamides, serum sickness, and thiouracil can give the anatomical picture of periarteritis nodosa. It is probably the conjugation of serum proteins with some other agent which proves injurious to some individuals and acts as allergen. No sulfonamides were given our patient. The drugs administered during her stay for chorea and her second admission were salicylates, cevitamic acid, penicillin and pyribenzamine.

The morphologic changes in Sydenham's chorea are remarkably insignificant. They consist mainly of hyperemia, moderate lymphocytic infiltration around the blood vessels, and degenerative changes of the striatum, as well as of the cortex, substantia nigra and dentate nuclei of the cerebellum.[3] That chorea is a manifestation of rheumatic fever is undisputed. Bruetsch [4] has called attention to the occurrence of rheumatic brain disease, an obliterating arteritis, as a late sequel to rheumatic fever. No mention of chorea is made in his reports.

Psychotic manifestations occurring in disseminated lupus are not uncommon. Daly [5] reported two cases, one with autopsy, of acute disseminated lupus erythematosus with central nervous system involvement. There occurred toxic delirium and shifting neurologic findings. At autopsy, a diffuse nonspecific encephalitis with extensive vascular damage was found. In one of Cluxton and Krause's [6] cases as in our case, there was a psychosis characterized by hallucinations and ideas of persecution.

Remissions in disseminated lupus are very frequent. They may be complete or partial and may last for years. Baehr and Pollack [2] report a patient who has had the disease for nine years and several patients who "recovered completely after a long and irregular illness which, at times, seemed as if it would end fatally." The cause of remissions is as yet unknown. Recovery is rare.[7]

It is probable that our patient had disseminated lupus at the time she was admitted for chorea. The rash on both palms, arthralgia, lymphadenopathy, and leukopenia point to that possibility.

The question as to whether rheumatic fever and disseminated lupus erythematosus are to be considered different clinical manifestations of a hyperergic state is not settled. Teilum [8] reviewed the problem and stated that "the primary fibroid degeneration of collagen connective tissue, though differing in intensity, extension and secondary mesenchymal reaction," is common to both diseases. These are essentially the changes defined by Klinge as "rheumatic." In contrast to rheumatic fever, however, Aschoff bodies are not found in disseminated lupus; nor are the "wire-loop" lesions and focal necrosis of glomerular loops, characteristic of disseminated lupus, seen in rheumatic fever. Teilum includes disseminated lupus in the group of diseases thought to be of allergic nature and calls it "pararheumatic," to imply that a state of hypersensitivity to various agents exists. Yet the disease is different clinically and morphologically from rheumatic fever in many respects. Baehr and Pollack also point out that they have never encountered a patient with disseminated lupus with eosinophilia, urticaria, asthma, or other clinical manifestations of allergy. They suggest that too many differences exist between the two diseases to warrant grouping them together into a common category.

The evidence here presented—namely, the typical picture of Sydenham's chorea in a Negro girl with a "rheumatic" history, uneventful and characteristic recovery from the choreic manifestations, and the subsequent appearance of the characteristic clinical picture of disseminated lupus erythematosus—suggests, however, a similar pathogenesis in a predisposed individual.

SUMMARY

A case of Sydenham's chorea, followed within six weeks by disseminated lupus erythematosus, is reported in a 17 year old Negro girl.

At autopsy, both rheumatic heart disease and disseminated lupus were demonstrated.

The simultaneous occurrence of both rheumatic fever and disseminated lupus and the close relationship of these diseases are briefly discussed.

ADDENDUM

After we submitted our manuscript, a similar case has come to our attention (von Albertini, A., and Alb, O.: Ueber die atypische verrucoese Endocarditis Libman-Sacks und ihre Beziehungen zum Lupus erythematodes acutus, Cardiologia 12: 1947, Fasc. 3.), a 17 year old girl with chorea minor who developed disseminated lupus. Two sisters of the patient suffered from chronic disseminated lupus erythematosus.

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2. Baehr, G., and Pollack, A. D.: Lupus erythematosus and scleroderma, J. A. M. A. 134: 1169, 1947.
3. Lewy, F. H.: Die Histopathologie der choreatischen Erkrankungen, Ztschr. f. d. ges. Neur. u. Psych. 85: 622, 1923.
4. Bruetsch, W.: Rheumatic brain disease, J. A. M. A. 134: 450, 1947.
5. Daly, D.: The nervous system in acute disseminated lupus erythematosus, J. Nerv. and Ment. Dis. 5: 461, 1945.
6. Cluxton, H. E., and Krause, L. A. M.: Acute disseminated lupus erythematosus, Ann. Int. Med. 19: 843, 1943.
7. Bauer, J., and Arndal, O.: Arthritic syndromes. II. Reiter's disease followed by endocarditis and lupus erythematosus disseminatus after sulfathiazole treatment, M. Rec. 159: 151, 1946.
8. Teilum, G.: Pathogenetic studies on lupus erythematosus disseminatus and related diseases, Acta med. Scandinav. 123: 126, 1946.

EDITORIAL

SOME OBSERVATIONS ON THE EOSINOPHIL

THE rôle which the eosinophil has lately been assigned as an indicator of adrenal cortical function, has once more focused the limelight on this elusive cell. This recent prominence has served to emphasize our ignorance of its function. Despite a considerable volume of investigative work directed at elucidating eosinophilic function, the cell has succeeded in guarding its secret well.

Although the origin of the eosinophil has been much disputed, it is now generally accepted that it develops, along with other members of the granulocytic series, from the extravascular myeloblast, and that specific granules develop at the promyelocyte stage. These increase in number through myelocytic and metamyelocytic stages, until the fully fledged granulocyte, with its complement of mature eosinophilic granules, is discharged, or rather makes its own pseudopodial way into the circulation.

What appears to be a fantastic and heretical theory of the origin and function of eosinophils was put forward by Duran-Jorda [1] of Barcelona in 1943. He claimed that lymphocytes in gastric and intestinal mucosae become eosinophils via intermediary Paneth cells; that eosinophil granules are preformed red cells; that eosinophils migrate from the mucosa to other tissues, where they burst and liberate red cells; and that the mononuclear remainder of the eosinophil becomes a lymphocyte, which returns to the gastrointestinal mucosa—and the cycle is repeated.

This hypothesis appears grotesque, and Duran-Jorda's work has for the most part gone unnoticed. But there is much logical thought behind his arguments, and these are backed by published photomicrographs which are hard to explain except by his postulates. One is tempted to wonder, however, if some of his photographs could be accounted for by the phenomenon of phagocytosis of hemoglobin by leukocytes.

Duran-Jorda has, however, followed up his original work with later and perhaps more persuasive publications. [2,3] He first confirmed his previous human observations by studying horse blood, and then decided that his point could be even more conclusively proved if it could be demonstrated with red blood cells of a characteristic shape; he therefore turned his attention to the camel. There he found that all the granules contained in eosinophil cells were as elliptical as the animal's erythrocytes. Granules of the basophil cells, on the other hand, were circular. Normoblasts were also circular, and Duran-Jorda finds it hard to believe that these cells, by the accepted ideas of erythrocyte formations, should be denucleated by some unknown process and then form themselves into elliptocytes. He further supports his findings in the camel by his observations in two patients, father and son, who had oval-

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[1] Duran-Jorda, F.: Formation of red corpuscles, Lancet 1: 186, 1943.
[2] Duran-Jorda, F.: The eosinophil cell: studies in horse and camel, Lancet 2: 451, 1948.
[3] Duran-Jorda, F.: Letter to the editor, Lancet 1: 672, 1949.

ocytosis.   In each case there was a fairly constant proportion between oval and round cells, and in the peripheral eosinophils oval granules were seen. In situations where these cells had burst and eliminated their granules, which were thereby easier to enumerate, there was seen to be the same existing ratio between oval and round granules.

Although this work has yet to be confirmed, it serves to emphasize that hemopoiesis is not as perfectly understood as we may be inclined to think. No one who is acquainted with the vicissitudes of medical history will wish to denounce Duran-Jorda's theories out of hand simply because they seem bizarre and unorthodox.   To avoid the too common scientific crime of ridiculing a new idea, we need only recall the derision that greeted Lister's perfectly correct though revolutionary ideas.   It may be noted in passing that, whether or not the eosinophilic granule proves in the final analysis to be a preformed red cell, it was shown as long ago as 1894 at least to contain iron.[4]   This finding has been amply confirmed since, but no satisfactory explanation of the function of iron in this situation has been forthcoming.   It may also be mentioned that Jacobsthal[5] observed that eosinophils are capable of extruding their granules.

Whether or not the hemopoietic rôle of the eosinophil is substantiated, it is undoubtedly not the sole function of these cells.   It has long been known, for instance, that the eosinophil has phagocytic properties which have been demonstrated for bacteria and other foreign material.   In any quest for further functions it is a necessary step to consider briefly what conditions produce an increase or decrease of circulating eosinophils.

As is well recognized, *allergic* conditions, such as asthma, hay fever, urticaria, angioedema, anaphylactic shock and serum sickness, are frequently marked by an eosinophilia.   *Dermatoses*, particularly of the bullous kind—pemphigus, dermatitis herpetiformis, erythema multiforme—are similarly associated with an increase in eosinophils.   *Infections*, such as scarlet fever, syphilis, and tuberculosis, especially of the lymph nodes, are not infrequently accompanied by an eosinophilia.   *Infestations* by parasites, especially those which invade the tissues, such as trichinosis, filariasis, and hydatid disease, but also those which are confined to the intestine, as ancylostomiasis, often cause an eosinophilia.   Certain *blood dyscrasias*—pernicious anemia, erythremia, myelocytic and eosinophilic leukemias—are frequently accompanied by increased eosinophils.   Among other causes of eosinophilia are *Hodgkin's disease*; *malignancies*, especially those involving the uterine cervix, serous surfaces and bones; other *diseases of bone*, including chronic osteomyelitis, Paget's disease, rickets and osteomalacia; *splenectomy* and *irradiation*. Many *drugs* cause it, among which emetine, whole liver, arsenic, tridione, potassium iodide, digitalis, gold, mercury, salicylates, penicillin, and strep-

[4] Barker, L. F.: On the presence of iron in the granules of the eosinophilic leucocytes, Bull. Johns Hopkins Hosp. **5**: 93, 1894.

[5] Jacobsthal, E.: Über Phagocytoseversuche mit Myeloblasten, Myelocyten und eosinophilen Leukocyten (mit Bemerkungen über den feineren Bau der eosinophilen Leukocyten), Virchow's Arch. f. path. Anat. **234**: 12, 1921.

tomycin may be mentioned.   Many of the *"collagen" diseases*—chorea, rheumatic fever, periarteritis, rheumatoid arthritis, Libman-Sacks disease—may be attended by an eosinophilia.   Then there are a few conditions where the eosinophilia is not an incidental, collateral finding, but a *sine qua non*—Loeffler's syndrome, tropical eosinophilia and familial eosinophilia.

It might justifiably be hoped that a study of such diseases as the last mentioned group, where the high eosinophil count is so cardinal a feature, might shed light on the function of this elusive cell.   But since Engel[6] in 1936 pointed out that Loeffler's own cases showed a seasonal incidence, and reported some cases of his own which he called "privet cough," more and more evidence has been accumulating to suggest that the syndrome is merely another allergic disease.   Thus it has been reported as caused by pollen; prontosil; various infections including tuberculosis, brucellosis, amebiasis; parasitic infestations including ascariasis, trichiniasis, cutaneous helminthiasis, filariasis and others.   And the consensus at the moment is overwhelmingly in favor of regarding the syndrome as an allergic complex.

Again in the case of tropical eosinophilia ("pulmonary eosinophilosis"), circumstantial evidence points towards an infection or infestation; for neoarsphenamine has proved a quick and specific cure.   The cause has not been finally identified, but if it is due to a microörganism or parasite, as the specificity of arsenotherapy suggests, there is good reason to incriminate the cheese mite[7, 8]; and filarial infestation has also been strongly suspected.[9, 10]   Thus the pursuit continues to revolve in allergic circles.

From a consideration in general of the many conditions which stimulate an increase in eosinophils, it is apparent that one function of the eosinophil must be related to the presence of foreign or abnormal protein.   It is natural, therefore, that a rôle of destruction or removal of unwanted protein should be attributed to it.   The protein may apparently be exogenous, as in diseases of allergy, infections and infestations.   Where non-protein drugs produce an eosinophilia it has been suggested that their molecules may combine with a serum protein and so act as a foreign protein.   Where conditions produce a local as well as circulating eosinophilia, a chemotactic influence of the exogenous protein on the eosinophil is suggested—as for example the eosinophils in the nasal mucus of hay fever, in the bronchial mucosa in asthma, or in the local site of a positive skin test.

In other situations the protein may presumably be derived from the subject's own tissues.   Thus the eosinophilia of skin diseases may be the result of absorption of epidermal proteins.   The destruction products of lympho-

[6] Engel, D.: Uber eine eigenartige anaphylakische Erkrankung der Lunge, Beitr. z. Klin. d. Tuberk. **87**: 239, 1936.

[7] Carter, H. F., Wedd, G., and D'Abrera, V. St. E.: Occurrence of mites (acarina) in human sputum and their possible significance, Ind. M. Gaz. **79**: 163, 1944.

[8] Soysa, E.: Eosinophilic respiratory syndrome: review of 100 cases, J. Royal Army Med. Corps **92**: 1, 1949.

[9] Van der Sar, A., and Hartz, H.: The syndrome, tropical eosinophilia and microfilaria, Am. J. Trop. Med. **25**: 83, 1945.

[10] Morton, P. H., and Jones, C. C.: Tropical eosinophilia with report of a case treated with penicillin, Ann. Int. Med. **31**: 1112, 1949.

cytes are claimed to be especially chemotactic for eosinophils, and this may account for both the local accumulation of eosinophils in lymph nodes and the circulating eosinophilia of Hodgkin's disease. Wallis [11] has recently suggested that the offending antigen in rheumatoid arthritis is a protein derived from the patient's own tissues. If this is a true concept of the pathogenetic mechanism of this and other "collagen" diseases, it may well be that the eosinophilia in these conditions is also elicited by the presence of perverted endogenous protein.

Dalton,[12] in a well reasoned paper, points out that it is unlikely that the mere presence of foreign protein can be the specific factor causing eosinophilia, and he puts forward an interesting hypothesis. He suggests that it is not the antigenic protein itself that calls forth the eosinophilic reaction, but antibody. He cites much circumstantial evidence to support this, and summarizes his theory as follows. In the sensitized body, contact with antigen provokes an antibody reaction. Antibodies, being chemotactic for eosinophils, produce a localized eosinophilia at the site of antigen invasion, and as eosinophil production is speeded up, a circulating eosinophilia also develops. At the local site of antigen-antibody reaction eosinophils are broken down with release of histamine which causes the symptoms of the allergic reaction. The resulting enhanced capillary permeability permits further flooding of the area with antibody, until all antigen is neutralized.

One drawback to this theory is the uncertain status of eosinophils as histamine-producers. It was hoped that the association of eosinophilia with allergic conditions might in some way be tied together by the common bond of histamine, but investigations in this direction have been inconclusive. In 1935 Barsoum and Gaddum [13] showed that histamine-like activity of blood was higher in corpuscles than in plasma. Code [14] then showed that 70 to 100 per cent of whole blood histamine-equivalent was to be found in the leukocyte layer of unclotted, centrifuged blood of many animals and of man. This he further tracked down to the granulocyte by the following stages.[15] First he found that neither equine nor human platelets yielded significant quantities of histamine. Then he excluded the lymphocyte by determining that neither an extract of rabbit's lymph nodes, nor the blood of lymphocytic leukemia, yielded appreciable quantities. Again monocytes, obtained from exudates, were free from histamine activity. It was concluded, therefore, that the granular series is the major source of blood histamine, and this was confirmed by finding that the histamine-equivalent of the blood of myelocytic leukemia was 20 to 200 times greater than the equivalent found in normal blood.

[11] Wallis, A. D.: The serum proteins in rheumatoid arthritis, Ann. Int. Med. 32: 63, 1950.
[12] Dalton, D. J.: The eosinophil leucocyte, eosinophilia and allergy: a hypothesis, Lancet 2: 607, 1949.
[13] Barsoum, G. S., and Gaddum, J. H.: The pharmacological estimation of adenosine and histamine in blood, J. Physiol. 85: 1, 1935.
[14] Code, C. F.: The source in blood of the histamine-like constituent, J. Physiol. 90: 349, 1937.
[15] Code, C. F.: The histamine-like activity of white blood cells, J. Physiol. 90: 485, 1937.

Next the neutrophils of dogs were found not to yield estimable quantities of active histamine, and the blood of one patient with a neutrophil leukocytosis likewise showed no increase in histamine activity; on the other hand, four patients with an eosinophilia showed a definite increase in histamine activity of the blood. Code therefore concluded cautiously that "the eosinophil is, at least in most cases, a source in blood of the histamine-like activity." He appreciated, however, that all cases of eosinophilia were not necessarily accompanied by an increase in histamine activity of the blood, and very recently it has been shown that only one in a series of eight patients with eosinophilia showed such an increase.[16] At the moment it must therefore be concluded that there is no proved positive correlation between eosinophilia and the level of blood histamine activity, especially as Jackson and Rose had also previously been unable to show any parallelism between histamine activity and varying levels of eosinophil count in the same patient.[17] Thus both Dalton's theory and the rôle of the eosinophil in histamine production must await further investigations for confirmation or disproof.

A consideration in turn of the causes of eosinopenia appears to afford little in the way of a clue to eosinophilic function, but introduces some interesting hormonal relationships. Thus Bertelli[18] showed that considerable eosinopenia could be produced in dogs by the injection of adrenaline. Later Cannon and his coworkers experimentally,[19] and Heilbrunn and Liebert[20] clinically, found that insulin hypoglycemia, unattended by shock, was characterized by considerable liberation of adrenaline—presumably in a physiological attempt to meet the emergency of a rapid falling blood sugar. More recently Godlowski[21, 22] has demonstrated that insulin hypoglycemia produces relief of asthma and with it an eosinopenia. These effects were assumed to be the result of adrenaline liberation. He corroborated this by showing that intravenous infusion of adrenaline produced a corresponding eosinopenia. He suggests that eosinopenia is a "sympathetic" reaction, and eosinophilia a "vagal" reaction. He also showed that during the adrenaline-induced eosinopenia, the eosinophil count in the marrow does not alter—indicating that this is, therefore, not the site of eosinophil retention.

[16] Valentine, W. N., Pearce, M. L., and Lawrence, J. S.: Studies on the histamine content of blood, with special reference to leukemia, leukemoid reactions and leucocytoses, Blood 5: 623, 1950.

[17] Jackson, I. J., and Rose, B.: Observations on the histamine content of cerebrospinal fluid in man, J. Lab. and Clin. Med. 34: 250, 1949.

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[19] Cannon, W. B., McIver, M. A., and Bliss, S. W.: Studies on the conditions of activity in endocrine glands. XIII. A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia, Am. J. Physiol. 69: 46, 1924.

[20] Heilbrunn, G., and Liebert, E.: Observations on the adrenaline level in the blood serum during insulin hypoglycemia and after metrazol convulsions, Endocrinology 25: 354, 1939.

[21] Godlowski, Z. Z.: Insulin shock treatment of bronchial asthma, British M. J. 1: 717, 1946.

[22] Godlowski, Z. Z.: Eosinopenia caused by adrenaline infusion and by insulin hypoglycemia, British M. J. 1: 46, 1948.

Laragh and Almy [23] have confirmed that eosinopenia follows the injection (subcutaneous in their experiments) of adrenaline and insulin; while White and his associates [24] have very recently shown that the eosinopenia produced by subcutaneous injection of adrenaline is preceded by an earlier rise in eosinophils. This tendency they found was more marked in subjects with a history of allergy. This primary rise in eosinophil count had not before been reported as such, but they quote supporting figures from other authors' experiments whose significance had apparently escaped previous notice.

Perhaps most interesting of all has been the gradual unfolding of the relationship between the circulating eosinophil and pituitary and adrenal cortical hormones. Early in the history of adrenocorticotropic hormone therapy, it was observed that the drug caused a depression in the number of circulating eosinophils. [25] This effect was presumably mediated through the adrenal cortex which was stimulated to secrete 11,17-oxysteroids. This is further confirmed by the fact that injection of these oxysteroids produces a similar eosinopenia. Thorn and his colleagues [26] have elaborated a test of adrenal cortical function on the basis of these findings—with absence or impairment of cortical function there is no reduction in circulating eosinophils following the administration of ACTH.

During the past decade much has been written concerning the value of cortical hormones in combating shock. It is therefore not surprising to find that the adrenal cortex functions energetically, as measured by depression of circulating eosinophils, in patients subjected to stress and trauma. Dalton and Selye have drawn attention to the fact that a marked eosinopenia accompanies the alarm reaction, [27] and gynecological surgery and myocardial infarction have both been shown to be attended by a marked depression in the eosinophil count. [28] Laragh and Almy [28] have confirmed the finding of postoperative eosinopenia, and a reduction in eosinophils has been shown to follow electrically induced convulsions. [29] Both eclampsia and labor have also been shown to produce a similar effect. [30] Roche and his colleagues, [31] who have yet to encounter a surgical patient who did not show a profound depres-

[23] Laragh, J. H., and Almy, T. P.: Changes in circulating eosinophils in man following epinephrine, insulin and surgical operations, Soc. Exper. Biol. and Med. 69: 499, 1948.

[24] White, C., Ling, T. H., and Klein, A. M.: The effect of administration of epinephrine on the leucocyte counts of normal subjects, Blood 5: 723, 1950.

[25] Hills, A. G., Forsham, P. H., and Finch, C. A.: Changes in circulating leucocytes induced by the administration of pituitary adrenocorticotropic hormone (ACTH) in man, Blood 3: 755, 1948.

[26] Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G.: A test for adrenal cortical insufficiency, J. A. M. A. 137: 1005, 1948.

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[29] Altschule, M. D., Parkhurst, B. H., and Tillotson, K. J.: Decreases in blood eosinophilic leucocytes after electrically induced convulsions in man, J. Clin. Endocrinology 9: 440, 1949.

[30] Davis, M. E., and Hulit, B. E.: Changes in circulating eosinophils in women during the menstrual cycle and reproduction, J. Clin. Endocrinology 9: 714, 1949.

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sion of eosinophils postoperatively, suggest that the test may perhaps be useful as a preoperative guide to prognosis—those showing poor eosinophil response preoperatively to ACTH administration are likely to have inadequate cortical function with which to counter the shock of surgery, and vice versa.

Another interesting finding which reveals the close relationship between hormone balance and eosinophil level is the fact that ovulation is accompanied by a fall in circulating eosinophils; and that eosinophil counts during the luteal phase of the menstrual cycle are lower than during the follicular phase.[30]

There are thus at least four hormones which depress the level of circulating eosinophils—insulin, adrenaline, ACTH and 11,17-oxysteroids. As insulin stimulates the liberation of adrenaline, and as it is believed that adrenaline stimulates the pituitary to produce ACTH, it is at least theoretically possible that all four hormones influence the eosinophil level by the same final mechanism. Exactly what that mechanism is, perhaps the near future will disclose, and then additional light may be shed on the eosinophil's function.

This brief review makes no pretense at being complete—it is consciously far from it. If it serves to gather together some of the threads of recent developments which involve the eosinophil, it will have fulfilled it purpose.

H. J. L. M.

REVIEWS

Coronary Circulation in Health and Disease. By DONALD E. GREGG, M.S., Ph.D., M.D., Chief Research Physician, Medical Department, Field Research Laboratory, Fort Knox, Kentucky. 227 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1950. Price, $4.50.

"It is a duty as well as a privilege for qualified investigators occasionally to summarize current trends in the form of a monograph so that workers in related fields may keep in touch with contemporary knowledge. In order to be of real value, such reviews require more than categorical statements of contradictory conclusions reached by different groups of investigators. It cannot be assumed and fairly appraised in relation to the experimental procedures employed. Unless this is done we are apt to confuse what can occur with that which does occur in the normally beating heart."

The author has succeeded admirably in fulfilling the purpose of this volume so clearly stated in this excerpt from the foreword by Dr. Carl J. Wiggers. The author's approach to the subject is a critical one, and the reports of various investigators are analyzed carefully. He first describes the anatomical features of the coronary circulation. The section on the experimental approaches to the coronary circulation is a particularly good one, in which are described the animal preparations and the apparatus employed for the measurement of cardiac pressures. It is pointed out how these technical methods influenced the findings in various experiments, and how different preparations may give apparently contradictory results. There is a chapter on the distribution of the coronary blood flow. The many determinants of the coronary blood flow are considered with respect to the experimental method, the results obtained and the validity of these results. Among the factors included are the coronary arterial blood pressure, the coronary venous pressure, the extra-vascular support, the effects of asphyxia, anoxia, hypercapnia, and myocardial ischemia on coronary inflow, the responses of the coronary circulation to augmented load, nervous influences, the possibility of reflex control of coronary blood flow, heart rate, temperature and blood viscosity, valvular lesions, shock, and the effects of various drugs. The last chapter deals with the coronary circulation in heart disease and heart failure.

This book is recommended not only to research workers in this field, but to the cardiologist and internist. For the last two, it provides a critical physiological basis for evaluating the many conflicting reports of investigations of the coronary circulation.

S. S.

Thrombosis In Arteriosclerosis of the Lower Extremities. By EDWARD A. EDWARDS, M.D., F.A.C.S., Diplomate of American Board of Surgery; Clinical Associate in Anatomy, Harvard Medical School; Instructor in Surgery, Tufts College Medical School; Consultant in Peripheral Vascular Disease, Joseph H. Pratt Diagnostic Hospital and Hospital of the Massachusetts Soldiers' Home; Chief of Vascular Clinic, Boston Dispensary. 74 pages; 14.5 × 22 cm. Charles C. Thomas, Publisher, Springfield, Illinois. 1950. Price, $2.00.

This is an excellent monograph on the problem of thrombosis in the arteriosclerotic limb.

A concise description of the etiology and pathology is given in addition to an extremely practical discussion of the clinical picture.

Treatment is discussed in detail and arguments advanced for lumbar sympathectomy, as well as for the use of heparin and Dicoumarol.

Considerable space is devoted to specific case reports, illustrating the course of this catastrophic disease and the author's mode of treatment.

This monograph is very well illustrated and indexed. It contains a brief but excellent bibliography.

G. H. Y.

Physiology of Heat Regulation and the Science of Clothing: Prepared at the Request of the Division of Medical Sciences, National Research Council. Edited by L. H. NEWBURGH, M.D., Professor of Clinical Investigation, The Medical School, University of Michigan. 467 pages; 15.5 × 24 cm. W. B. Saunders Co., Philadelphia. 1949. Price, $7.50.

This book attempts to describe the response of the heat regulatory mechanism of the human body through the whole range of climatic conditions existing on the earth's surface. It is divided into two large sections. Part I—The body's response to the climatic environment. Part II—Clothing a thermal barrier.

The first part consists of eight contributions by men, each of whom is very familiar with one or more phases of the general problem. Each chapter presents in great detail the latest information on its subject with extensive and authoritative documentation. In addition it is well written, holding one's interest from beginning to end. The point of departure is civilization since the thermal adaptation of human beings is described. The term "civilization" is used in the ordinary anthropological sense to mean the culture of a literate people. Three civilizations of the entire world's history are used, the Egyptian, the Sumerian and Mayan. The reviewer can heartily agree with the comments on the Egyptian and Sumerian civilizations from his own studies and sojourns in the land of Egypt and Sumer. As for Egypt, who can rightly ask what civilization has done better, even though it may be that Sumer reached the goal of civilization first. In any case, history of these three civilizations points to the same lesson, that men can do hard physical work and creative work in the hot, dry or moist country. They can prosper and retain all their vigor even in the desert. The white man's adaptation is not due to the ingenuity of his mind, but rather to the pliability of his body. This is certainly true in view of our present knowledge. His dress is a compromise between cultural tradition, practical utility and passing fashion. In addition to this it is also an expression of a particular way of life and set of institutions. All this is a part of the challenge and response reaction that seems to be fundamental in the genesis of civilization so well depicted by Toynbee. These conclusions are very favorably presented in this section of the book.

The remaining chapters of the first section are an able presentation of the physiology of heat regulation. This emphasizes the effective mechanism of heat control that begins with the hypothalamus through which the sensory and reflex mechanisms are mediated. Between the hypothalamus and the periphery we have the venae comites. Known since the last century their importance is being more and more realized. Their function is apparently warming and cooling the blood going to and from the periphery. Over the periphery of the body we have the subcutaneous tissue in addition to the skin. Both these tissues act as an insulating layer, whose maximal efficiency is said to be equal to a similar thickness of cork. In the skin there are the sweat glands, chiefly those controlling thermal sweat, namely, the eccrine glands. In the fingers and toes are found small arteriovenous anastomoses often referred to as the glomera. These dilate and constrict depending upon the needs of the organism. The fingers and toes are literally the radiators of the body, far more efficient than a radiator in the ordinary sense of the word. In construction the fingers and toes are roughly small cylinders. This form increases their ability to radiate heat. Finally, there is the tendency when one is chilled to develop so called "goose skin," *cutis anserina*. This roughness lessens the amount of heat loss in contrast to the amount that would occur

if the skin remained smooth. It is apparent from the physiology that heat to be of any value in warming a patient should be applied to the body, rather than to the hands and feet. When vasoconstriction is present in the hands and feet as a result of loss of body temperature, the reflex mechanism cannot be reversed by application of heat to the feet. This fact alone is of fundamental importance in the treatment of peripheral vascular disease. In terms of rectal temperature, the body can successfully withstand a deviation of 10° Centigrade on the cool side and 6° Centigrade on the hot side. One is impressed after reading this section of the book with the precision and efficiency of the human body in adjusting itself to its environment.

The second part of the book is devoted entirely to the subject of clothing as a thermal barrier. The discussion is concerned with those properties of clothing which are known to be related to human comfort and efficiency. The main emphasis is on laboratory tests on properties of clothing in terms of effectiveness and comfort. It is observed that the warmth of the various materials depends far more on the air held in the interstices of the cloth than on the properties of the fiber itself. The insulation value of clothing decreases during exercise, but usually to an extent insufficient to prevent sweating. The conclusion is drawn that no single system of clothing protection can be said to be completely superior to all others. However, each has advantages and disadvantages. The Eskimos' fur clothing is perhaps the most efficient from the standpoint of weight, utility and simplicity, but it is costly and scarce. No doubt the great advances in clothing design in the future will revolve around artificial control of the temperature of the individual's own immediate environment.

In conclusion this book is a must on the shelf of everyone interested in peripheral vascular disease; a reference book for medical students, the specialist in peripheral vascular disease and physiologist. In addition, those interested in clothing connected with the armed forces can hardly afford not to be familiar with its contents.

L. A. M. K.

Mitchell-Nelson's Textbook of Pediatrics. 5th Ed. Edited by WALDO E. NELSON, M.D., with the collaboration of 63 contributors. 1,658 pages; 18 × 26.5 cm. W. B. Saunders Co., Philadelphia. 1950. Price, $12.50.

The science and art of the Practice of Pediatrics has become so vast and complex that a textbook of this calibre which so completely and fully covers this subject is, indeed, a welcome one. For the practitioner of general medicine and of pediatrics, and particularly for the teacher and student, this work is extremely helpful and is indeed a true source and reference book.

The entire book has been brought up to date and much has been rewritten. It has been no easy task to bring all the information on child care, development, growth, and diseases of children into one volume.

New information or completely rewritten sections on the following subjects are found in this fifth edition: Growth and Development, Congenital Malformations, Inborn Errors of Metabolism, Parenteral Fluid Therapy, Anesthesia for Children, Infection, Immunity, and Allergy in Relation to Pediatrics, Streptococcal Infections, The Use of the Viral Diagnostic Laboratory, as well as a number of individual viral diseases, Histoplasmosis, Congenital Heart Disease, and Mental Deficiency.

Other sections have been revised, as those on Drug Therapy, the Newborn Infant, the Infectious Diseases, the Blood, Bones, and Joints, Endocrine Disturbances, and Adolescence; Mental Growth, Development and Psychologic Disorders, and Psychological Aspects of Adolescence, Impaired Hearing and Eye Diseases.

The latest methods of therapy with the newer antibiotics are well described. The publishers have produced a handsome volume. The illustrations are clear and informative and the type easily read.

A. H. F.

A Textbook of Medicine for Nurses. 5th Ed. By E. NOBLE CHAMBERLAIN, M.D. 491 pages; 14 × 22.5 cm. Oxford University Press, New York. 1949. Price, $6.00.

Dr. Chamberlain has condensed into 491 pages the cursory presentation of many diseases and situations. The subjects included would ordinarily constitute several texts, for example: principles of bacteriology, dietetics, general nursing, materia medica and pharmacology. It is doubtful if these sections add to the value of the book, since they lack the details essential to an understanding of even basic facts.

The relative significance of the disease, it seems, has not determined its prominence. Cholera, hydrophobia and plague, though checked as less important, are given as much space as rheumatic fever and diabetes; smallpox is given twice as much.

The usual form of organization in discussing the disease entities is: (a) the nature of the disease, (b) the symptoms, and (c) the treatment. Again, the author is brief and curt with no discussion of underlying factors. To illustrate: on page 190, "The course of the disease (pneumonia) is greatly modified by the use of sulfonamides or penicillin, which shortens the period of pyrexia and abolishes many symptoms in 24 to 48 hours."

The acute communicable diseases of childhood—scarlet fever, measles, etc.—constitute one of the better sections of the book. The presentation is more detailed and there is one or more pictorial illustrations for each entity. On the whole, illustrations, which total 73, are good.

The major systems—respiratory, cardiovascular, etc.—are introduced by brief, comprehensive reviews of the physiology of the respective system. Unfortunately, however, physiological principles upon which nursing procedures are developed are not considered. In keeping with this policy, clinical laboratory studies are given merely as directions for performing a few simple tests, which tests would probably rarely, if ever be done by the nurse.

It is unlikely that this book will suffice as a basic text in medical nursing. It fails to provide for an intelligent understanding of the disease or situation. It directs rather than informs the student. This reviewer believes that the book will serve its maximum usefulness as a quick reference where details are not expected.

S. M. F.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adrenal Cortex: Transactions of the First Conference, November 21–22, 1949. Edited by ELAINE P. RALLI, New York University College of Medicine; Associate Editors: KONRAD BLOCK, University of Chicago School of Medicine, and GREGORY PINCUS, Worcester Foundation for Experimental Biology. 189 pages; 23.5 × 15.5 cm. 1950. Josiah Macy, Jr. Foundation, New York. Price, $2.00.

The Antihistamines: Their Clinical Application. By SAMUEL M. FEINBERG, M.D., Associate Professor of Medicine, Chief of Division of Allergy and Director of Allergy Research Laboratory; SAUL MALKIEL, Ph.D., M.D., Assistant Professor of Medicine, Director of Research, Allergy Research Laboratory, and ALAN R. FEINBERG, M.D., Clinical Assistant in Medicine, Attending Physician in Allergy Clinic, Northwestern University Medical School. 291 pages; 18.5 × 12.5 cm. 1950. The Year Book Publishers, Inc., Chicago. Price, $4.00.

Biological Standardization. 2nd ed. By J. H. BURN, Professor of Pharmacology in the University of Oxford; D. J. FINNEY, Lecturer in the Design and Analysis of Scientific Experiment in the University of Oxford; and L. G. GOODWIN, Member of the Staff of the Wellcome Laboratories of Tropical Medicine. 440 pages; 22.5 × 14 cm. 1950. Oxford University Press, New York. Price, $6.75.

Cerebral Palsy. By JOHN F. POHL, M.D., Orthopedic Surgeon, Michael Dowling School for Crippled Children, Minneapolis. 244 pages; 21 × 14 cm. 1950. Bruce Publishing Company, Saint Paul, Minnesota. Price, $5.00.

Clinical Examination of Patients, with Notes on Laboratory Diagnosis. By JOHN FORBES, M.D., M.R.C.P., Physician to the Wrexham Hospitals, etc., and W. N. MANN, M.D., F.R.C.P., Assistant Physician to Guy's Hospital. 323 pages; 22.5 ×14.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $4.50.

Expert Committee on Environmental Sanitation: Report on the First Session, Geneva, 12–17 September 1949. World Health Organization Technical Report Series No. 10. 33 pages; 24 × 16 cm. (paper-bound). 1950. World Health Organization, Geneva. Price, 25¢.

Expert Committee on Tuberculosis: Report on the Fourth Session, Copenhagen, 26–30 July 1949. World Health Organization Technical Report Series No. 7. 20 pages; 24 × 16 cm. (paper-bound). 1950. World Health Organization, Geneva. Price, 15¢.

Expert Committee on the Unification of Pharmacopoeias: Report on the Fifth Session, Geneva, 26 September–5 October 1949. World Health Organization Technical Report Series No. 12. 12 pages; 24 ×16 cm. (paper-bound). 1950. World Health Organization, Geneva. Price, 10¢.

Inter-Allied Conferences on War Medicine, 1942–1945, Convened by the Royal Society of Medicine. Honorary Editor: MAJOR-GENERAL SIR HENRY LETHEBY TIDY, K.B.E., M.D., President of the Inter-Allied Conferences, etc.; Assistant Editor: J. M. BROWNE KUTSCHBACH, M.B., B.CH., D.P.H. 531 pages; 22.5 ×14.5 cm. 1950. Staples Press, Inc., New York. Price, $5.00.

Lehrbuch der Röntgendiagnostik. By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER. 426 pages; 28.5 × 20 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Preis der 1. Lieferung: DM 66.–

The Liver: Porta Malorum (The Gateway to Disease). By KASPER BLOND, M.D. (Vienna), L.R.C.P., L.R.C.S. (Ed.), L.R.F.P.S. (Glas.), Late First Assistant of I and II Surgical Dept., allg. Krankenhaus, Vienna, etc., and DAVID HALER, M.B., D.C.P. (Lond.), Hon. Consulting Pathologist, Westminster Hospital (All Saints Urological Centre), etc. 268 pages; 22.5 × 14 cm. 1950. The Williams and Wilkins Company, Baltimore. Price, $5.00.

Malignant Disease and Its Treatment by Radium. Volume III, 2nd ed. By SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., Surgeon, Westminster Hospital, etc.; with a Foreword by SIR ERNEST ROCK CARLING, F.R.C.P., F.R.C.S., F.F.R., Consulting Surgeon and Vice President, Westminster Hospital. 446 pages; 23.5 × 15.5 cm. 1950. The Williams and Wilkins Company, Baltimore. Price, $12.50.

The Modern Treatment of Asthma, with Special Reference to Gold Therapy. By L. BANSZKY, M.D. (Berlin), L.M.S.S.A. (Lond.). 135 pages; 19.5 × 12.5 cm. 1950. The Williams and Wilkins Company, Baltimore. Price, $2.50.

Physician's Handbook. 6th ed. By MARCUS A. KRUPP, M.D., Assistant Clinical Professor of Medicine, Stanford University School of Medicine, etc.; NORMAN J. SWEET, M.D., Assistant Professor of Medicine, University of California School of Medicine, San Francisco; ERNEST JAWETZ, Ph.D., M.D., Associate Professor of Bacteriology and Lecturer in Medicine and Pediatrics, University of California School of Medicine, San Francisco; and CHARLES D. ARMSTRONG, M.D., Clinical Instructor in Medicine, Stanford University School of Medicine. 380 pages; 18 × 18 cm. 1950. University Medical Publishers, Palo Alto, California. Price, $2.50.

Pneumoconiosis: Beryllium, Bauxite Fumes, Compensation—Leroy U. Gardner Memorial Volume. Edited by ARTHUR J. VORWALD, M.D., Director of The Trudeau Foundation and The Saranac Laboratory; with the collaboration of MANFRED BOWDITCH, A.B., THOMAS M. DURKAN, M.E., and THEODORE C. WATERS, L.L.B. (Sixth Saranac Symposium.) 659 pages; 24.5 × 16 cm. 1950. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $7.50.

Researches on the Radiotherapy of Oral Cancer: Medical Research Council Special Report Series No. 267. By CONSTANCE A. P. WOOD and J. W. BOAG (with P. HOWARD-FLANDERS, A. GLÜCKSMANN, L. H. GRAY and F. G. SPEAR). 148 pages; 24 ×15.5 cm. (paper-bound). 1950. His Majesty's Stationery Office, London. Price, 12s. 6d. net.

Significance of the Body Fluids in Clinical Medicine. By L. H. NEWBURGH, M.D., Professor of Clinical Investigation, University of Michigan Medical School, Ann Arbor, Michigan; assisted by ALEXANDER LEAF, M.D., Instructor in Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan. 76 pages; 22.5 × 14.5 cm. (limp leather binding). 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $2.00.

Steroid Hormones and Tumors: Tumorigenic and Antitumorigenic Actions of Steroid Hormones and the Steroid Homeostasis: Experimental Aspects. By ALEXANDER LIPSCHUTZ, M.D., Formerly Professor of Physiology, Hon. M. Roy. Soc. Med. (Endocrinol.), etc. 309 pages; 23.5 ×15.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Tuberculosis and Other Problems of Pediatrics: The Abraham Flexner Lectures—Series Number Ten. By ARVID WALLGREN, M. D., Professor of Pediatrics, The Royal Caroline Medical Institute, Stockholm, Sweden. 108 pages; 21 × 14 cm. 1950. Published for Vanderbilt University by The Williams & Wilkins Company, Baltimore. Price, $2.25.

The Urinary Function of the Kidney. By A. V. WOLF, Ph.D., Associate Professor of Physiology, Albany Medical College, Union University. 363 pages; 24 × 15.5 cm. 1950. Grune & Stratton, Inc., New York. Price, $7.50.

COLLEGE NEWS NOTES

32ND ANNUAL SESSION
OF THE
AMERICAN COLLEGE OF PHYSICIANS
ST. LOUIS, MO.
April 9–13, incl., 1951

General Headquarters: Kiel Municipal Auditorium, St. Louis, Mo.

Program: General Sessions, Morning Lectures and Convocation—in charge of William S. Middleton, M.D., F.A.C.P., President, Madison, Wis. Clinics, Television, Panels, Entertainment and Banquet—in charge of Ralph A. Kinsella, M.D., F.A.C.P., General Chairman, St. Louis, Mo.

Hotel Reservations: Application form for housing accommodations available through the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. Nineteen hotels on approved list, all of which have guaranteed a certain number of rooms at specified rates. All reservations must finally be made on the official form through the Hotels Convention Reservation Bureau, Room 406, 911 Locust St., St. Louis 1, Mo.

A.C.P. POSTGRADUATE COURSES, AUTUMN OF 1950

By the time of the publication of this notice the following courses will have been concluded, or at least will be under way:

No. 1, INTERNAL MEDICINE; SELECTED SUBJECTS. R. R. Snowden, M.D., F.A.C.P., Director; University of Pittsburgh Medical Center, Pittsburgh, Pa., September 25–30.

This course was greatly over-subscribed and very few non-members could be accommodated.

No. 2, PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE. Eugene A. Stead, Jr., M.D., F.A.C.P., Director; Duke University School of Medicine, Durham, N. C., October 9–14.

This course also was greatly over-subscribed and a very limited number of non-members could be accommodated.

No. 3, CRITICAL PROBLEMS IN INTERNAL MEDICINE. Wright Adams, M.D., F.A.C.P., Director; University of Chicago School of Medicine, Chicago, Ill., October 23–27.

This course with a capacity for 100 is adequate to accommodate all member applicants and several non-members.

No. 4, CLINICAL ALLERGY. Robert A. Cooke, M.D., F.A.C.P., Director; Roosevelt Hospital Institute of Allergy, New York, N. Y., October 23–November 3.

This two weeks' clinical course was limited to 8 registrants and all places were taken.

The following courses still remain on the schedule and applications for registration are still being accepted. However, Course No. 6 will be over subscribed. It is too early to state what facilities will be available for non-members in the other courses.

No. 5, RECENT DEVELOPMENTS IN MEDICINE. M. M. Wintrobe, M.D., F.A.C.P., Director; University of Utah College of Medicine, Salt Lake City, Utah, November 6–11.

No. 6, PERIPHERAL VASCULAR DISEASES INCLUDING HYPERTENSION. Walter F. Kvale, M.D., F.A.C.P., Director; and Edgar V. Allen, M.D., F.A.C.P., Nelson W.

Barker, M.D., F.A.C.P., John E. Estes, M.D., Edgar A. Hines, Jr., M.D., F.A.C.P., and Richard M. Shick, M.D., F.A.C.P., Co-Directors; Mayo Clinic and Mayo Foundation, Rochester, Minn., November 27–December 2.

No. 7, GASTRO-ENTEROLOGY. Henry L. Bockus, M.D., F.A.C.P., Director; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., December 4–9.

No. 8, SELECTED ASPECTS OF CLINICAL HEMATOLOGY. William Dameshek, M.D., F.A.C.P., Director; New England Center Hospital and Tufts College Medical School, Boston, Mass., December 11–16.

No. 9, MODERN TRENDS IN DIAGNOSIS AND TREATMENT OF HEART DISEASE. William G. Leaman, Jr., M.D., F.A.C.P., Director; Woman's Medical College of Pennsylvania and Other Philadelphia Institutions, Philadelphia, Pa., January 22–27, 1951.

For course outlines, registration forms and other information, address the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

A.C.P. REGIONAL MEETINGS—AUTUMN, 1950—SPRING, 1951 SCHEDULE

Several of the annual regional meetings have been concluded on the following schedule. They were marked by enthusiasm and gratifying attendance. The programs have been uniformly excellent. It is customary for the Executive Offices of the College to publish and mail the programs to the members in the territory covered by the meetings. There are so many of these regional meetings that space does not permit of publication of the programs in the Annals. Furthermore, many of the programs are not published more than five or six weeks in advance of the meeting and adequate time is not available for their prior publication in this journal. Any interested members, outside of the particular territory represented by the meeting, may be placed on the mailing list to receive programs.

POSTGRADUATE PROGRAM OF THE MEDICAL SOCIETY OF THE STATE OF NEW YORK

One of the most extensive extramural postgraduate programs is carried on by the Medical Society of the State of New York under the Council Committee on Public Health and Education of which Dr. Theodore J. Curphey is Chairman as well as Director of Postgraduate Medical Education. The program is aimed at meeting the educational needs of the various county medical societies. Part of the object is to provide subjects of sufficiently broad interest to attract attendance of societies as a whole. They have found that topics of broad interest, having greater appeal to the general practitioner, are more welcome than lectures on highly specialized subjects. An organized concurrent series of lectures on certain related topics is more popular than single lectures on unrelated subject matter. Each county medical society is asked to designate a chairman, with a functioning committee, the chairman to serve for a period of not less than two years. The committee also arranges instruction for a one-day session designated as a "teaching day," which is a combination of clinics, demonstrations and lectures for a whole day. Lecturers are asked to substitute a clinic for a lecture if appropriate patients and facilities are available and if requested by the group. Traveling expenses of speakers are paid by the Medical Society of the State of New York and honoraria for speakers are paid by the New York State Department of Health.

Certain recognized teachers, institutions and societies collaborate with the State Medical Society in arranging the programs and selecting the speakers. Their course outline book shows that the program covers practically every branch of medicine. Heart disease programs are arranged by Dr. Clarence E. De La Chapelle, F.A.C.P., of New York University Postgraduate Medical School, and by the New York Heart Association; general medicine by Dr. A. F. R. Andresen, F.A.C.P., and Dr. William

Calendar of Regional Meetings

Region	City	Dates	Governor or Chairman	Official Guest(s) from Board of Regents
NORTH DAKOTA	Minot	September 9, 1950	Robert B. Radl, Governor / Paul J. Breslich, Local Chairman	LeRoy H. Sloan, Regent
MONTANA-WYOMING	Billings	September 15-16, 1950	Harold W. Gregg, Governor / Wayne Gordon, Arrangements	William S. Middleton, President
WESTERN PENNSYLVANIA	Pittsburgh	September 27, 1950	Charles W. Morton, Governor	Maurice C. Pincoffs, President-Elect
OKLAHOMA-ARKANSAS	Tulsa	September 30, 1950	Wann Langston, Governor for Oklahoma / A. A. Blair, Governor for Arkansas	Walter L. Palmer, Regent and Chairman, Board of Governors / E. R. Loveland, Executive Secretary
MISSISSIPPI	Jackson	October 7, 1950	John G. Archer, Governor	William S. Middleton, President / E. R. Loveland, Executive Secretary
NORTHERN CALIFORNIA	San Francisco	October 13, 1950	Dwight L. Wilbur, Governor	Maurice C. Pincoffs, President-Elect
SOUTHERN CALIFORNIA	Los Angeles	October 14, 1950	Leland Hawkins, Governor	Maurice C. Pincoffs, President-Elect
WESTERN NEW YORK	Rochester	October 14, 1950	Edward C. Reifenstein, Governor / William S. McCann, General Chairman	William S. Middleton, President / E. R. Loveland, Executive Secretary
ARIZONA	Tucson	October 14, 1950	Leslie R. Kober, Governor	LeRoy H. Sloan, Regent

Calendar of Regional Meetings—*Continued*

Region	City	Dates	Governor or Chairman	Official Guest(s) from Board of Regents
PACIFIC NORTHWEST (Oregon, Washington, Idaho, Alberta and British Columbia)	Portland	October 27–28, 1950	Howard P. Lewis, Governor for Oregon George H. Anderson, Governor for Washington Samuel M. Poindexter, Governor for Idaho John W. Scott, Governor for Alberta and British Columbia	Cyrus C. Sturgis, Regent
NEW JERSEY	Trenton	November 1, 1950	Edward C. Klein, Jr., Governor	William S. Middleton, President
PUERTO RICO	San Juan	November 5, 1950	Rafael Rodriguez-Molina, Governor	Maurice C. Pincoffs, President-Elect
UTAH	Salt Lake City	November 11, 1950	Fuller B. Bailey, Governor	Walter L. Palmer, Regent and Chairman, Board of Governors
MIDWEST (Illinois, Indiana, Iowa, Michigan, Minnesota, Ohio and Wisconsin)	Madison	November 18, 1950	Karver L. Puestow, Governor for Wisconsin, General Chairman Walter L. Palmer, Governor for Northern Illinois Charles H. Drenckhahn, Governor for Southern Illinois James O. Ritchey, Governor for Indiana Benjamin F. Wolverton, Governor for Iowa Douglas Donald, Governor for Michigan Wesley W. Spink, Governor for Minnesota Charles A. Doan, Governor for Ohio	William S. Middleton, President LeRoy H. Sloan, Regent George Morris Piersol, Secretary-General E. R. Loveland, Executive Secretary

Calendar of Regional Meetings—*Continued*

Region	City	Dates	Governor or Chairman	Official Guest(s) from Board of Regents
NORTH CAROLINA	Chapel Hill	December 8, 1950	Elbert L. Persons, Governor	(Pending)
KENTUCKY	Lexington	December 9, 1950	J. Murray Kinsman, Governor	(Pending)
MIDSOUTH (Louisiana, Tennessee and Texas)	Memphis	January 12-13, 1951	William C. Chaney, Governor for Tennessee, General Chairman Thomas Findley, Governor for Louisiana David W. Carter, Jr., Governor for Texas	William S. Middleton, President George Morris Piersol, Secretary-General E. R. Loveland, Executive Secretary
SOUTHEASTERN (Alabama, Florida, Georgia and South Carolina)	Charleston	January 26-27, 1951	Robert Wilson, Jr., Governor for South Carolina, General Chairman E. Dice Lineberry, Governor for Alabama William C. Blake, Governor for Florida Carter Smith, Governor for Georgia	William S. Middleton, President E. R. Loveland, Executive Secretary
COLORADO	Denver	February 20, 1951	Ward Darley, Governor	(Pending)
DELAWARE	Wilmington	February 22, 1951	Lemuel C. McGee, Governor	(Pending)
NEBRASKA	Omaha	February 7, 1951	Joseph D. McCarthy, Governor	(Pending)
KANSAS	Wichita	March 16, 1951	William C. Menninger, Governor	William S. Middleton, President
MARYLAND AND DISTRICT OF COLUMBIA	Washington	(Pending)	John Minor, Governor for District of Columbia Wetherbee Fort, Governor for Maryland	(Pending)

Dock, F.A.C.P., also by Dr. Edward C. Reifenstein, F.A.C.P., and Dr. Richard H. Lyons, F.A.C.P., of Syracuse University College of Medicine, etc. Other coöperating and participating agencies include the Division of Cancer Control of the New York State Department of Health, the Commissioner for Tuberculosis Control of the New York State Department of Health, the Albany Hospital, New York University College of Medicine, New York Diabetes Association, Long Island College of Medicine, Cornell University Medical College, Columbia University College of Physicians and Surgeons, New York Medical College, University of Buffalo School of Medicine, Albany Medical College, University of Rochester School of Medicine and Dentistry, Hospital for Joint Diseases of New York City, New York State Psychiatric Institute, The Ophthalmological Foundation, New York Polyclinic Medical School and Hospital, and others.

The field covered includes, with their subdivisions, Cardiology, Rheumatic Fever, Cancer, Vascular Disorders, Surgery, Diseases of the Chest, Kidney Diseases, Disorders of Metabolism, Arthritis and Rheumatism, Obstetrics, Gynecology, Pediatrics, Geriatrics, General Medicine, Anesthesiology, Orthopedic Surgery, Neuropsychiatry, Gastro-enterology, Ophthalmology, Otolaryngology, Dermatology and Syphilology, Allergy, Proctology, Public Health and Preventive Medicine, Physical Medicine, Industrial Health, Forensic Medicine, Medical Aspects of Radioactive Materials, Nutrition, Alcoholism, Plasma Therapy and Blood Substitutes and Derivatives, etc., etc. Additionally, a directory of available medical motion picture films is provided.

GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE

The Twenty-Third Graduate Fortnight of the New York Academy of Medicine was held at the Academy on October 9 through 20, 1950, and the program was especially built around the musculo-skeletal system. Dr. Currier McEwen, F.A.C.P., Dean of New York University College of Medicine, was the Chairman of the Fortnight Committee. Dr. Richard H. Freyberg, F.A.C.P., was Chairman of the Committee on Hospital Clinics.

TULANE UNIVERSITY OF LOUISIANA SCHOOL OF MEDICINE
OFFERS POSTGRADUATE COURSES

The Division of Graduate Medicine of Tulane University of Louisiana School of Medicine, New Orleans, schedules the following postgraduate courses for the session, 1950–1951:

Common Infections of Warm Climate—October 16–27.
Therapeutics As Applied to General Practice—November 6–10.
Electrocardiography—November 27–December 8.
Slit Lamp Microscopy and Gonioscopy—November 27–December 2 and December 4–9.
Gynecology (for Specialists)—January 8–13.
General Surgery and Traumatology—January 15–20.
Public Health Seminar—January 22–27.
Ocular Pathology—February 12–17.
Pediatrics (for Specialists)—February 12–17.
Ocular Pharmacology and Therapeutics—February 19–24.
Recent Advances in Internal Medicine—March 12–17.
Obstetrics—April 2–7.
The Specialties as Applied to General Practice—April 9–14.
Psychiatry and Neurology—June 18–23.
Cardiology—February 19–March 2.

Sterility and Endocrinology—Date to be announced.
Tropical Medicine for Latin Americans—Date to be announced.

POSTGRADUATE COURSE IN DISEASES OF THE CHEST

The American College of Chest Physicians has announced a postgraduate course in Diseases of the Chest, organized with the coöperation of members of the Staffs of the New York City Medical Schools and Hospitals, to be held at the Hotel New Yorker, New York City, November 13–18, 1950. The matriculation fee is $50.00 and inquiries should be sent to the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Ill.

RESEARCH FELLOWSHIPS IN THE FIELD OF ARTHRITIS

Research fellowships in the basic sciences related to the study of arthritis are offered by the Arthritis and Rheumatism Foundation. The annual stipend is from $4,000 to $6,000, beginning July, 1951. Inquiries should be addressed to the Arthritis and Rheumatism Foundation, 535 Fifth Avenue, New York 17, N. Y., before January 1, 1951.

THE HELEN HAY WHITNEY FOUNDATION

Under deed executed May 10, 1943, a Charitable Trust was established by Helen Hay Whitney for the primary purpose of continuing after her death financial contributions to certain charities in which she was particularly interested during her lifetime. Capital funds provided immediately and for the future aggregated approximately $1,000,000. The Helen Hay Whitney Foundation was organized within the framework of this Trust on February 10, 1947, with the contribution of $5,000,000 by Mrs. Charles S. Payson, daughter of Helen Hay Whitney. The immediate purpose of the Foundation is to stimulate and support research pertinent to the solution of the problem of rheumatic fever and rheumatic heart disease.

Dr. T. Duckett Jones of Boston accepted the appointment of Medical Director which office was created in May, 1947. The initial research grants of the Foundation became effective on October 1, 1947.

In Dr. Jones' first report of the Helen Hay Whitney Foundation are discussed the underlying principles of operation and of objectives along with a report on an extensive survey of needs and methods. Eighteen grants have been voted by the Foundation to the end of 1949. Most grants have been made for a three-year period, and the optimal duration of support is now being studied. Greater volume of funds to date have been designated to support the work of established or career investigators.

Six research fellowships have been awarded, two of which constitute advanced fellowships, the recipients being more experienced than is the case in the usual initial research fellowship award.

ANNOUNCEMENT OF VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held at Columbus, Ohio, May 24, 25 and 26, 1951, provided essays of sufficient merit are presented in competition.

The essays may cover either clinical or research investigations and should not exceed three thousand words in length. They should be presented in English and a

typewritten double-spaced copy in duplicate sent to the Corresponding Secretary, Dr. George C. Shivers, 100 E. St. Vrain St., Colorado Springs, Colo., not later than March 1, 1951. A place will be reserved on the program of the annual meeting of the Association for presentation of the Prize Award Essay by the author, and the essay will be published in the annual Proceedings of the Association.

Defense Department Announces Priorities for Calling Medical and Dental Reserve Officers to Active Duty

A system of priorities has been established under which Army, Navy and Air Force medical and dental reserve officers will be called to active duty in the current military expansion program.

Excluded from the new priority plan are: (1) members of "organized" reserve units—that is, those assigned to TO/E, T/D and other organized units which are authorized paid drill and training periods and point credit toward retirement benefits; (2) Those pursuing a 12-month medical internship, whose recall will be delayed until completion of this training.

The first group to be called includes medical and dental reserve officers who received all or part of their professional education in the Army's ASTP program or the Navy's V-12 program, and who have had no military service as medical or dental officers. Substantially all of this group will be ordered to active duty before calls are made for other classifications.

In the second priority group are those who participated in the ASTP or V-12 programs and who have had subsequent military service, with those having the least service to be called first.

The third priority includes all other reserve officers.

The Army, Navy and Air Force will furnish information in advance to Dr. Richard L. Meiling, Director of Medical Services, Department of Defense, whenever the departments plan to call reserve medical or dental officers to active duty, with these plans subject to review by the Director of Medical Services and the Secretary of Defense prior to issuance of orders to the reservists.

Exceptions to the priority system may be authorized by the Director of Medical Services when individuals with special qualifications are required to meet military needs, since older physicians and dentists highly skilled in certain specialties must be provided from time to time.

In carrying out this policy, the three military departments have been instructed to review their previous procedures in issuing orders for call to active duty, in order that those individuals who have received orders but have not yet reported for duty may be reconsidered on the basis of this priority system.

Air Force to Commission Medical Professional Women

Women physicians, dentists, veterinarians, as well as technical specialists for duty in the Medical Service Corps may now receive reserve commissions in the Air Force, and may apply for extended active duty at Air Force installations. Women so commissioned will receive the same pay and allowances as male officers. The grade in which they will be appointed will also be based on the same considerations of age and professional qualifications as male officers. The grades will range from first lieutenant to colonel. Women physicians will be eligible to participate in the Air Force sponsored civilian intern program under which physicians receive the pay and allowances of a first lieutenant in the Air Force while completing their internships at civilian hospitals with the understanding that they will serve on active duty for two months for every month spent as an Air Force-sponsored intern in the civilian hospital.

To be eligible for reserve commissions, women physicians and other Medical Service Corps specialists must hold appropriate degrees from accredited schools approved by the Surgeon General, United States Air Force. They must be citizens of the United States. They may be married, but may not have dependents less than eighteen years of age. Applications should be addressed to the Surgeon General, Headquarters, U. S. Air Force, Washington 25, D. C.

Four Fellows of the College were among the guest speakers at the Annual Clinical Conference of the Kansas City Southwest Clinical Society, Kansas City, Mo., October 2–5. The participating Fellows and their subjects were: Dr. Arthur Grollman, F.A.C.P., Dallas, Tex., "Acute Anuria: Pathogenesis and Treatment"; Dr. Francis E. Senear, F.A.C.P., Chicago, Ill., "Eczematoid Conditions of the Hands"; Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, Calif., "Management of Gastrointestinal Bleeding"; and Dr. Irving S. Wright, F.A.C.P., New York, N. Y., "Modern Treatment of Coronary Thrombosis."

Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, and Dr. George Baehr, F.A.C.P., President and Medical Director of the Health Insurance Plan of Greater New York, have been appointed to the newly created Board of Hospitals, which is the policy-making agency for the Department of Hospitals of the City of New York.

The National Gastroenterological Association held its Fifteenth Annual Convention in New York, October 9–11, 1950, under the presidency of Dr. Horace W. Soper, F.A.C.P., St. Louis, Mo. Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, Que., Canada, President-Elect, assumed office as President during the session. The Convention was followed by a course in Postgraduate Gastroenterology, October 12–14, 1950. Numerous Fellows and Associates of the American College of Physicians were among the speakers on the program.

Dr. Maud L. Menten, F.A.C.P., for many years Professor of Pathology at the University of Pittsburgh School of Medicine, has now retired and is residing permanently in New Westminster, B. C., Can. Dr. Menten is a Life Fellow of the College.

Dr. John S. L. Browne, Jr., F.A.C.P., Professor of Medicine at McGill University Faculty of Medicine, was the principal speaker on the Scientific Program of the first Annual Scientific-Social Meeting of the California Society of Internal Medicine which was held in Yosemite on September 23 and 24, 1950. Dr. Browne conducted a symposium on recent developments and experiences with Cortisone and A.C.T.H.

Dr. Jacob C. Geiger, F.A.C.P., Director of Public Health for the City and County of San Francisco was recently appointed Consultant in Public Health to the Surgeon General of the Navy for the San Francisco and Pacific areas.

The antibiotic laboratories of Hektoen Institute for Medical Research of Cook County Hospital has been named for the late Dr. Italo F. Volini, F.A.C.P., Chicago, who died June 24, 1950. Dr. Volini was one of the Institute's founders, a member of its board of trustees and a pioneer in antibiotic therapy.

The promotions of Dr. Jerome W. Conn, F.A.C.P., and Dr. John McFarland Sheldon, F.A.C.P., to the rank of professor of Internal Medicine have been announced by the University of Michigan Medical School.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been elected a Foreign Corresponding Member of The National French Gastro-enterological Society at its annual session in Paris. Dr. Goldstein recently received a testimonial certificate award from the New Jersey Gastro-enterological Society at its annual meeting, as the Gastro-enterologist and Medical Historian of the Year.

The Minnesota State Medical Association will hold its 98th Annual Meeting in Rochester, Minn., April 30, and May 1 and 2, 1951. All scientific and technical exhibits will be housed in the Rochester Municipal Auditorium.

Dr. James S. Glotfelty (Associate), on August 20, 1950, became the Manager of the Veterans Administration Hospital at Lebanon, Pa. Formerly, he was Chief of the Neuropsychiatric Section of the Veterans Administration District Office at St. Louis, Mo.

At the First International Congress on Cardiology held in Paris, France, September 3–9, 1950, Dr. George R. Herrmann, F.A.C.P., Galveston, Tex., Dr. William J. Kerr, F.A.C.P., San Francisco, Calif., and Dr. Paul D. White, F.A.C.P., Boston, Mass., were among the speakers.

Dr. Edward A. Strecker, F.A.C.P., Professor of Psychiatry, University of Pennsylvania School of Medicine, will present, for the third successive year, a series of two lecture courses to the approximately 1,400 cadets at the U. S. Military Academy, West Point, N. Y. The general theme of the lectures is Military Neuropsychiatry and the topic is "The Men You Will Command." Dr. Strecker is Consultant to the Surgeons General of the U. S. Army and the U. S. Navy.

Captain Christopher C. Shaw (MC), USN, F.A.C.P., was recently presented with the Certificate of Merit and the Selective Service Medal by Major General Lewis B. Hershey, Director of Selective Service, in appreciation of his services as Consulting Internist to the State of Vermont Draft Board during 1940 and 1941. Captain Shaw was also awarded the Louis Livingston Seaman Prize by the Association of Military Surgeons for this article on "Dramamine Trials in the U. S. Navy," which was selected for its exceptional usefulness from among the articles published in *The Military Surgeon* during the past year.

Dr. Marion A. Blankenhorn, F.A.C.P., Regent, American College of Physicians, and Professor of Medicine, University of Cincinnati College of Medicine, was one of the guest speakers on the program of a postgraduate course in general medicine conducted on September 21–23 by the Frank E. Bunts Institute and the Cleveland Clinic. Dr. Blankenhorn's topic was "The Rickettsial Diseases."

Dr. Ewald W. Busse (Associate), was recently appointed Director of the Division of Psychosomatic Medicine, University of Colorado School of Medicine.

Seven Fellows of the American College of Physicians presented addresses at the twenty-fifth Annual Clinical Congress of the Connecticut State Medical Society and the Yale University School of Medicine which was held in New Haven, September 12–14. Among the speakers were Dr. Harris Isbell, F.A.C.P., Lexington, Ky.; Dr. Paul R. Hawley, F.A.C.P., Chicago, Ill.; Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.; Dr. John H. Foulger, F.A.C.P., Wilmington, Del.; Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill.; Dr. Chester S. Keefer, F.A.C.P., Boston, Mass.; and Dr. Irving W. Wright, F.A.C.P., New York, N. Y. Dr. Elmer L. Henderson, President of the American Medical Association, was the guest of honor.

Colonel Charles L. Leedham, (MC), USA, F.A.C.P., was recently appointed Chief of Medical Service at Tripler General Hospital, Honolulu, T. H.

Dr. Francis R. Manlove, F.A.C.P., Philadelphia, Pa., was recently appointed Associate Secretary of the Council on Medical Education and Hospitals of the American Medical Association.

Among the speakers at the annual meeting of the Washington State Medical Association held in Spokane, September 10–13, were Dr. Raymond B. Allen, F.A.C.P., Seattle, Wash.; Dr. George F. Lull, F.A.C.P., Chicago, Ill.; Dr. Robert H. Williams, F.A.C.P., Seattle, Wash.; and Dr. William B. Castle, F.A.C.P., Boston, Mass.

Dr. Arthur C. DeGraff, F.A.C.P., Professor of Therapeutics, New York University College of Medicine, was recently chosen Vice Chairman of the American Council on Rheumatic Fever of the American Heart Association.

Captain Bartholomew W. Hogan, (MC), USN, F.A.C.P., recently assumed command of the U. S. Naval Medical School, National Naval Medical Center, Bethesda, Md.

Dr. James E. McCormack (Associate), has been appointed Associate Dean of the New York University Postgraduate Medical School.

Dr. William I. Gefter, F.A.C.P., Philadelphia, Pa., was recently promoted to the position of Clinical Associate Professor of Medicine by the Woman's Medical College of Pennsylvania. At the same time, Dr. Maurice Sones (Associate), Philadelphia, Pa., was promoted to Clinical Assistant Professor of Medicine.

Dr. Robert N. Armen (Associate), has recently been appointed Chief of Medical Service, Veterans Administration Hospital, Altoona, Pa.

Dr. Tinsley R. Harrison, F.A.C.P., was recently appointed Professor of Medicine and Acting Dean of The Medical College of Alabama.

Dr. Paul B. Beeson, F.A.C.P., Chairman of the Department of Medicine, Emory University School of Medicine, has been appointed Associate Dean to assist Dr. R. Hugh Wood, F.A.C.P., Dean.

Among the speakers at the annual meeting of the Georgia Heart Association held September 15–16 in Atlanta were Dr. Tinsley R. Harrison, F.A.C.P., Birmingham, Ala.; Dr. Edgar Hull, F.A.C.P., New Orleans, La.; Dr. Eugene B. Ferris, F.A.C.P., Cincinnati, Ohio; and Dr. John P. Merrill (Associate), Boston, Mass.

Dr. George F. Lull, F.A.C.P., Chicago, Ill., addressed the annual meeting of the Wyoming State Medical Society in Cody, September 7–9. Dr. Lull's subject was "National Legislation Affecting Medical Associations."

At the annual session and postgraduate conference of the Michigan State Medical Society held in Detroit, September 20–22, Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Pa., spoke on "The Elderly Patient"; Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Pa., spoke on "Newer Developments in Atomic Medicine"; Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, spoke on "The Leukemic States: Their Differentiation and Specific Management"; Dr. Priscilla White, F.A.C.P., Boston, Mass., spoke on "NPH-50 Insulin."

Dr. Richard D. Friedlander, F.A.C.P., Associate Clinical Professor of Medicine, University of California Medical School, was recently appointed a member of the Executive Committee of the Committee on Cardiovascular Clinics of the American Heart Association. This committee has recently prepared a new set of standards of minimum requirements for those cardiovascular clinics desiring approval by the American Heart Association.

Dr. James S. Simmons, F.A.C.P., Brigadier General (Retired), Medical Corps, U. S. Army, Dean and Professor of Public Health, Harvard School of Public Health, has just been appointed a member of the Armed Forces Medical Advisory Committee. The Committee serves as an advisory body to the Secretary of Defense on policies affecting the medical services of the three military departments.

Colonel John M. Welch (MC), USA, F.A.C.P., recently assumed command of the Valley Forge General Hospital, Phoenixville, Pa.

George R. Herrmann, M.D., F.A.C.P., of the University of Texas Medical Branch, Galveston, addressed the First International Congress on Internal Medicine at Paris, September 11–14, on "The Heart in Acromegaly." He also addressed the First International Congress on Cardiology at Paris, September 3–9. On his return from Paris, he proceeded to Ann Arbor, Mich., where he delivered a paper on the program of the Centennial Celebration of the University of Michigan Medical School, and while in Ann Arbor, he participated in the teaching of the graduate course in Clinical Internal Medicine from October 7 to 14.

Among the speakers at the joint annual meeting of the New Hampshire Medical Society and the Vermont State Medical Society, held in Bretton Woods, N. H., September 9–12, were Dr. Marian W. Ropes, F.A.C.P., Boston, Mass.; Dr. Howard A. Rusk, F.A.C.P., New York, N. Y.; and Dr. Donald S. King, F.A.C.P., Boston, Mass. The guest speaker at the annual banquet was Dr. Paul R. Hawley, F.A.C.P., Chicago, Ill.

OBITUARIES

DR. FRANCISCO DE P. MIRANDA

Francisco de P. Miranda, M.D., F.A.C.P., Governor of the American College of Physicians for Mexico, died April 28, 1950. The Universidad Nacional de Mexico has lost with his passing one of its outstanding members who dedicated most of his activities to the teaching of Clinical Medicine and of Endocrinology—he was, in fact, one of the pioneers of these branches in his country.

Dr. Miranda was born in Puebla, Mexico, February 6, 1890. He received his medical degree at the School of Medicine, Universidad Nacional de Mexico in 1914. This was about the time of one of the stages of the Mexican Revolution, and the country was in the process of suffering deep social changes. This period of Dr. Miranda's life was characterized by his participation in sanitary work. He was one of the members of the brigade which fought an outbreak of typhus in 1915 and another in 1918. Thereafter he became chief sanitary officer in Matamoros and a delegate of the Department of Health to several medical congresses and conventions.

In 1921 he initiated his teaching career and medical investigations, mainly in the fields of Endocrinology and Nutrition. In 1930 he was designated Professor of Clinical Medicine at the Universidad Nacional de Mexico, and later on he occupied the first chair of the professorship of Endocrinology. He was recognized immediately as an authority in this specialty.

Regarding his clinical work, he was Chief of a Service of Internal Medicine at the Hospital General de Mexico and Consulting Endocrinologist and Nutriologist in the Instituto Nacional de Cardiologia. From 1940 until his death Dr. Miranda became profoundly interested in the nutritional problems of Mexico, and he undertook several investigations in these matters. It was in great part due to his efforts that the Instituto de Nutriologia was founded in 1943. It was in this institution that bromatologic research and evaluation of the social aspects of nutrition of the Mexican population were carried out. Dr. Miranda was its Director almost to the time of his death. Additionally, he was Chairman of the Comisión de Alimentación of the Department of Health of which he was also an adviser.

Dr. Miranda published a number of important scientific and medical papers, among them being "Hypoproteinosis" in the Journal of the American Medical Association, "La Alimentacion de Mexico," "Nutrition and Endocrinology," etc.

Dr. Miranda was a member of many societies and organizations both at home and abroad. In Mexico, he was a member and Chairman (1936–37) of the Academia Nacional de Medicina. In the United States, he was a Fellow of the American College of Physicians since 1933, and its Governor for Mexico since 1941; also an honorary member of the American Medical Association since 1947; corresponding member of the New York Academy of Medicine; and member of the American Diabetes Association.

Dr. Miranda was recognized not only by his medical work, but through other human qualities and virtues that were known to all—his kindness, his vast culture, his sense of humor, his human understanding—these will be remembered by all who knew him.

SALVADOR ZUBIRAN, M.D., F.A.C.P.,
Mexico, D. F.

DR. LESTER TAYLOR

Lester Taylor, M.D., F.A.C.P., Cleveland, Ohio, was born in Verona, N. Y., August 18, 1884. He received his A.B. degree from Oberlin College in 1906 and his M.D. degree from Johns Hopkins University School of Medicine in 1910. There

followed postgraduate studies in internal medicine, with special reference to cardiology, in Bern, Munich and Vienna. From 1929 to 1942 he was Visiting Physician at St. Luke's Hospital, becoming Acting Director for the period 1942–45. He was Director of Medicine at St. Luke's from 1945 until his death on April 11, 1950, from coronary thrombosis.

Dr. Taylor became a Diplomate of the American Board of Internal Medicine in 1937 and was elected a Fellow of the American College of Physicians in November, 1947. He was President of the Cleveland Academy of Medicine (1934–35) and was the Founder and President of the Cleveland Health Museum.

Dr. Taylor was an extraordinarily gifted individual. While attending college and medical school he partially supported himself as a professional pianist. He also played semi-professional baseball as a means of furthering his medical education. His academic career was interrupted by participation in the Mexican Expedition just prior to World War I, and his subsequent volunteering for overseas service after this country became involved resulted in an extraordinary record in the Medical Corps of the Army of the United States. Following the conclusion of World War I, he returned to Cleveland and entered the private practice of medicine.

Dr. Taylor was an idealist who had an extraordinary capacity for work and great personal charm. He interested himself in the clinical training of the younger physicians at St. Luke's Hospital where as Chief of the Medical Service he had an opportunity for sharing his medical wisdom.

His death occurred suddenly while on vacation at Pinehurst, N. C., at the height of his active medical career.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. JOSEPH E. KNIGHTON

Dr. Joseph Edward Knighton, F.A.C.P., died of coronary thrombosis in Shreveport, La., on March 9, 1950, after a long and useful career. He was born in Claiborne Parish, La., in 1870, received the M.D. degree in 1899 from the University of Nashville Medical Department and the following year became associated in practice with Dr. J. C. Willis of Homer, La. In 1910 this partnership moved to Shreveport where a few years later they formed the Shreveport Clinic. In 1928 the Willis-Knighton Clinic was formed when the senior partners and others purchased the Tri-State Hospital, the success of which required the addition of numerous physical facilities.

Dr. Knighton served terms as President of the Tri-State Hospital and the Louisiana State Medical Society, and as Vice-President of the Southern Medical Association. For many years he was a member of the Louisiana State Board of Medical Examiners, and a staff member of the Shreveport Charity Hospital and the Pines Sanatorium. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians since 1923, and was Governor for Louisiana from 1933–1942.

His devout Christian character was recognized by all who knew him. He served on the Board of Deacons of the First Baptist Church and was its Senior Member. He took an active interest in civic affairs, and was a member of the board of directors of the Chamber of Commerce for several years. He enjoyed the work and fellowship of the Rotary Club and was a Shriner. His friendly smile, his coöperative attitude, and his desire to aid the younger men in medicine, together with his devotion to his profession and to his church, will cause him to be long remembered. His son, Dr. James E. Knighton, F.A.C.P., is his able successor.

THOMAS FINDLEY, M.D., F.A.C.P.,
Governor for Louisiana

INDEX TO ADVERTISERS

October, 1950

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. The ANNALS will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by volume or by year. Volumes will consist of approximately 1,300 pages. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.25. Members of the American College of Physicians receive the ANNALS OF INTERNAL MEDICINE in connection with the payment of annual membership dues, of which nine dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.